

Heart failure as presenting manifestation of cardiac involvement in systemic lupus erythematosus

N.E. van der Laan-Baalbergen¹, S.A. Mollema², H. Kritikos³, A. Schoe⁴, T.W.J. Huizinga¹, J.J. Bax², D.T. Boumpas³, J.M. van Laar^{1*}

Departments of ¹Rheumatology, ²Cardiology and ⁴Intensive Care, Leiden University Medical Center, the Netherlands, ³Department of Rheumatology, University of Crete Medical School, Heraklion, Greece, *corresponding author (Musculoskeletal Research Group, Institute of Cellular Medicine, Newcastle University, Newcastle upon Tyne, United Kingdom): tel.: +44 191-222 71 39, fax: +44 191-222 54 55, e-mail: j.m.van-laar@ncl.ac.uk

ABSTRACT

Background: Heart failure in systemic lupus erythematosus (SLE) is rare, and its long-term outcome is unknown. The aim of this study was to analyse the long-term outcome of six SLE patients with heart failure as first manifestation of cardiac involvement and to review previously reported cases.

Methods: We conducted a retrospective chart review of SLE patients from two tertiary referral centres who presented between 1999 and 2004 with clinical and echocardiographic signs of heart failure as their first manifestation of cardiac involvement. Details of the clinical presentation and follow-up and serial findings at echocardiography were collected. A retrospective review of the literature was performed using the PubMed database.

Results: Six cases were identified who presented with heart failure, as confirmed by echocardiography (left ventricular ejection fraction (LVEF) ranging from 23 to 37%). Treatment with high-dose glucocorticoids, cytotoxic treatment (azathioprine in one patient, cyclophosphamide in five patients), intravenous immunoglobulins (in one patient) and temporary inotropic support (two patients) resulted in complete resolution of symptoms and improvement of LVEF, with a mean follow-up of 77 months (range 43 to 113). Twenty-one additional cases of heart failure as manifestation of cardiac involvement in SLE have been reported, most with favourable short-term outcome following institution of immunosuppressive therapy.

Conclusions: Heart failure is a rare but life-threatening manifestation of cardiac involvement in SLE. Long-term outcome can be excellent when aggressive treatment is instituted promptly.

KEYWORDS

Cardiac involvement, heart failure, systemic lupus erythematosus

INTRODUCTION

Heart failure is a rare but potentially life-threatening complication of myocarditis due to systemic lupus erythematosus (SLE).^{1,2} With timely therapy almost full recovery of cardiac function can be achieved. Post-mortem studies from the 1950s and 1960s found an average prevalence of myocarditis in 57%, but after the introduction of corticosteroid therapy this percentage decreased to 7%. The pathogenesis is thought to be mediated by immune complex formation and complement activation.³ Granular deposits of complement and immunoglobulin have been demonstrated in myocardial blood vessel walls and along muscle bundles. Focal interstitial plasma cell and lymphocyte infiltrates are seen with fibrinoid degeneration of collagen fibres and small foci of myocardial fibrosis, possibly leading to cardiac dysfunction. The diagnosis depends largely on clinical suspicion and echocardiography. Myocarditis may present clinically with fever, dyspnoea, palpitations, nonexertional chest pain, resting tachycardia that is disproportionate to the patient's temperature, gallop rhythms, new cardiac murmurs, cardiomegaly and peripheral oedema. Sinus tachycardia and nonspecific ST-T segment changes are frequently noted on the electrocardiogram. With echocardiography, left ventricular (LV) dysfunction can be observed, reflected by global or regional wall motion abnormalities, a decrease in LV ejection fraction (LVEF) and an increase in LV volumes

(indicating LV dilatation or remodelling).⁴⁻⁶ Apart from systolic LV dysfunction, diastolic dysfunction has been reported as well.⁷ Echocardiography is also essential to detect valvular lesions and pericardial effusion, which can occur in conjunction with myocarditis.⁸ Endomyocardial biopsy may distinguish between acute myocarditis and other causes of cardiomyopathy, although its sensitivity and specificity for the diagnosis of lupus myocarditis are not known.⁹ Current treatment strategies are empirical rather than based on clinical trials, and long-term outcome data are lacking. In the present study, we describe six patients from two tertiary referral centres who presented with life-threatening heart failure as a first cardiac manifestation of SLE, but experienced a good clinical response after immunosuppressive therapy with a mean follow-up of 77 months (range 43 to 113 months).

PATIENTS AND METHODS

We identified six patients by retrospective chart review who presented with heart failure secondary to myocardial involvement of SLE between January 1999 and November 2004 at Leiden University Medical Center, the Netherlands (patients 1-4), and University of Crete Medical Center, Greece (patients 5, 6), both tertiary referral centres. SLE was defined according to the 1997 American College of Rheumatology classification criteria.¹⁰ Demographic data, duration of disease, relevant clinical features, immunological data, 2D echocardiographic data and response to therapy were recorded. The diagnosis of SLE myocarditis was based on a clinical presentation of heart failure, confirmed by echocardiography. All patients were treated with supportive therapy (diuretics, oxygen, inotropics when required) and intravenous methylprednisolone pulse therapy (1000 mg on three consecutive days), followed by oral prednisone. Five out of six patients also received intravenous cyclophosphamide pulse therapy (750 mg/m² or less in case of kidney dysfunction). The response to therapy was assessed clinically and by echocardiography with a mean follow-up of 77 months.

RESULTS

All patients had severe heart failure with LV ejection fraction below 40% (range 23 to 37%). In addition, mild to moderate mitral regurgitation was observed in all patients on echocardiography. Two patients were treated on the intensive care unit with inotropic therapy and mechanical ventilation, one patient also received intra-aortic balloon pump counterpulsation (IABP) and another patient needed continuous veno-venous haemofiltration (CVVH). Five patients had an elevated serum creatinine and proteinuria,

while patients 1, 2 and 4 also had dysmorphic erythrocytes. Five patients had detectable antiphospholipid and/or anticardiolipin antibodies.

Patient 1

A 19-year-old woman with a history of arthralgias, was admitted in October 2004 because of pancytopenia (haemoglobin (Hb) 4.8 mmol/l, leucocytes 1.2×10^9 , thrombocytes 32×10^9), and fever. Bone marrow analysis was inconclusive. On admission, she reported no specific complaints. Physical examination was unremarkable except for bradypnea, a temperature of 38.6°C and two small cervical lymph nodes. Laboratory results showed normal serum creatinine, folic acid, vitamin B12, thyroid function, slightly elevated liver enzymes and on urinalysis 2+ proteinuria and erythrocyturia; antinuclear antibody (ANA) was positive. A repeat bone marrow examination was slightly hypocellular. Aplastic anaemia, myelodysplastic syndrome or acute myeloid leukaemia were excluded. Bacterial and viral cultures of serum and cerebral spinal fluid remained negative and computed tomography (CT) and magnetic resonance imaging (MRI) of the cerebrum were unremarkable. She recovered spontaneously and was discharged 12 days later. Ten days after discharge she was readmitted because of fever 39°C, nausea and vomiting, dyspnoea without palpitations or thoracic pain. On examination, her mental state was normal. Her blood pressure was 120/85 mmHg, heart rate 110 beats/min, temperature 37.3°C, her central venous pressure was normal and respiration frequency 14/min. On cardiac auscultation a gallop rhythm was heard without murmurs. On examination of the lungs no bibasilar breath sounds could be heard, on percussion there was a dullness in the lower lung fields, there were no rales. Mild peripheral oedema was observed. She had no signs of arthritis. Laboratory results showed an erythrocyte sedimentation rate (ESR) of 134 mm/1st hour, Hb 5.3 mmol/l, mean cell volume (MCV) 91 fl, reticulocytes 9%, leucocytes $1.7 \times 10^9/l$ (74% granulocytes), thrombocytes $90 \times 10^9/l$, creatinine 93 $\mu\text{mol/l}$, albumin 24 g/l, creatine phosphokinase (CPK) and troponin T were normal (50 U/l and $< 0.01 \mu\text{g/l}$ respectively). Antibodies against double-stranded (ds) DNA, Smith (Sm) antibodies and immunoglobulin M and G (IgM and IgG) anticardiolipin (aCL) antibodies were positive, lupus anticoagulans was negative and complement levels were very low. Dysmorphic erythrocytes were present at urinalysis and a proteinuria of 11 g/24 h was measured. Renal biopsy was not performed because of thrombocytopenia. Chest X-ray showed cardiomegaly and some pleural effusion. Echocardiography showed diffuse hypokinesia of the left ventricle, 3 cm pericardial effusion with systolic collapse of the right atrium, diastolic collapse of the right ventricle and mitral valve inflow variation $>30\%$. Drainage of 700 ml pericardial fluid was performed. Examination of the pericardial fluid revealed 0.5 leucocytes/ power field, no malignant cells

were found. Cultures remained negative (bacterial, fungal, tuberculosis). She was treated with furosemide, perindopril, carvedilol, acenocoumarol, intravenous methylprednisolone (1000 mg for three days) and cyclophosphamide 1350 mg (750 mg/m²). Culture-negative fever persisted and cardiac function deteriorated, necessitating inotropic therapy on the intensive care unit. Upon intravenous treatment with ten pulses of cyclophosphamide, two courses of high-dose methylprednisolone for three days and three courses of immunoglobulins (36 g/day, four days) her cardiac function gradually improved with LVEF increasing from 25 to 50%. At the time of last follow-up (September 2008) her cardiac function was stable and her renal function normal without proteinuria.

Patient 2

A 37-year-old woman with a history of ANA-positive, anti-dsDNA negative, rheumatoid factor negative, non-erosive polyarthritis for 11 years, treated with hydroxychloroquine, presented in July 1999 with exertional dyspnoea, fever and rash. The diagnosis of active SLE was made on the basis of ANA positivity, positive antiphospholipid antibodies, biopsy-proven glomerulonephritis (interstitial necrotising vasculitis with thrombosis and full house immunofluorescence, but with insufficient glomeruli for classification), pleuritis, and focal vasculitis in a skin biopsy, while other causes of pleuritis and nephritis were excluded. Antibodies against dsDNA, SSA and SSB were negative, while anti-ENA, anti-Jo and ribonucleoprotein (RNP) were weakly positive. IgM and IgG aCL were strongly positive. At echocardiography, diffuse hypokinesia was found, the LVEF measured 27% and mild mitral regurgitation was observed. CPK was normal (13 U/l). Following treatment with furosemide, enalapril, nifedipine, ascal, prednisolone 60 mg, and intravenous cyclophosphamide pulse therapy (12 x 1250 mg) she made a full recovery and went into remission in 2001. In November 2005 echocardiography showed an LVEF of 42% with normal dimensions. At the last follow-up in January 2007 she was still in remission on enalapril 10 mg daily and acetylsalicylic acid 100 mg daily.

Patient 3

A 40-year-old woman with a history of deep venous thrombosis, was admitted in October 2000 because of dyspnoea, alopecia, weight loss, muscle weakness, rash and disturbed vision. She developed cardiogenic shock and also had positive blood cultures with *Staphylococcus aureus* due to phlebitis but heart failure persisted after treatment with antibiotics (flucloxacillin). Echocardiographic examination demonstrated severe LV dysfunction (LVEF 23%) with moderate mitral regurgitation. Significant coronary artery stenosis was excluded on invasive coronary angiography. Endomyocardial biopsy of the left ventricle showed no signs

of vasculitis, immunofluorescence on immunoglobulins and complement was negative. CPK was normal (59 U/l). Findings of renal biopsy were compatible with lupus nephritis World Health Organisation (WHO) classification II. MRI of her cerebrum showed abnormalities compatible with SLE and she had retinal cotton wool spots as signs of vasculitis. Mild autoimmune thyroiditis was present, for which she received substitution with thyroxin. She was ANA, ENA, RNP, Sm positive, SSA, SSB and anti-dsDNA negative, and strongly positive for IgM and IgG aCL. She experienced no improvement after treatment with intravenous methylprednisolone pulses (1000 mg on three consecutive days) and azathioprine for 20 days. Impressive improvement was seen, however, after several intravenous pulses of cyclophosphamide (1185 to 1500 mg, 750 mg/m²). After treatment with eight pulses of cyclophosphamide her SLE went into remission with gradual normalisation of her heart function (LVEF 52% and 63% in December 2002 and June 2006 respectively). At the last follow-up in June 2008 she was doing well, on thyroxin 75 µg daily, enalapril 20 mg twice daily, hydroxychloroquine 200 mg twice daily, and acenocoumarol.

Patient 4

A 22-year-old woman, had been treated successfully for chronic myeloid leukaemia (CML) with hydroxyurea and α -interferon when she presented in November 1998 with polyarthritis, fever 39°C, purple skin lesions and myalgia. A diagnosis of SLE was made on the basis of leukopenia, positive ANA, antibodies against dsDNA and antiphospholipids, positive aCL, low complement levels, pleural effusion and leucocytoclastic vasculitis. Treatment with 60 mg prednisolone and azathioprine was initiated, and α -interferon discontinued. Two months later she was readmitted because of dyspnoea. Perfusion scintigraphy revealed a perfusion/ventilation mismatch in the right lung, for which anticoagulant therapy was started. Nevertheless, she remained dyspnoeic and fatigued, and was readmitted in February 1999. CPK was slightly elevated (101 U/l, normal up to 55 U/l). She was treated with intravenous methylprednisolone pulses 3 x 1000 mg, and switched to oral prednisolone in conjunction with azathioprine 125 mg daily. She was treated with mechanical ventilation and inotropic therapy and also with CVVH for renal failure as a result of lupus nephritis (WHO IIIA) and acute tubulus necrosis (ATN) after hypotension. Echocardiography demonstrated a severely depressed LV function (LVEF 25% in February 1999) with mild mitral regurgitation. Azathioprine was replaced by cyclophosphamide 65 mg daily (1 mg/kg iv), which was switched to intravenous cyclophosphamide pulse therapy (1300 mg, 750 mg/m²) two weeks later. On recent echocardiography LVEF was 51% without mitral regurgitation. In May 2001 a relapse of CML was

diagnosed, and imatinib 400 mg daily was started, upon which the CML went into remission. In June 2008 her CML and SLE were still in remission.

Patient 5

A 38-year-old woman, was diagnosed with SLE in March 2003 on the basis of photosensitivity, malar rash, arthritis, oral ulcers, and Raynaud's phenomenon. ANA, anti-dsDNA antibodies and aCL were negative. Her disease was well controlled with hydroxychloroquine 400 mg once daily when she was admitted in October 2004 for surgical treatment of haemorrhoids under regional anaesthesia. Approximately three hours after surgery she presented with dyspnoea, tachypnoea, chest pain, bloody sputum, hypotension and tachycardia. An ECG showed inverted T waves in various leads. Serum troponin was positive (9.8 ng/ml, normal <1.5). Echocardiography revealed a depressed LVEF (37%) with global hypokinesia, but no pericarditis. No evidence of lupus nephritis was present. On the basis of these findings a working diagnosis of lupus myocarditis was made and treatment instituted with intravenous methylprednisolone pulses (1 g on three sequential days), followed by oral prednisone (30 mg daily), azathioprine (150 mg daily) and hydroxychloroquine (400 mg daily), which led to a complete recovery. Follow-up echocardiography in November 2004 showed normalisation of LVEF (60%). She was still doing well at the last follow-up visit in May 2008.

Patient 6

A 37-year-old woman, was diagnosed with SLE in June 1984 on the basis of a malar rash, photosensitivity, arthritis, chorea, positive ANA, anti-dsDNA antibodies and aCL. She was successfully treated for lupus nephritis (WHO class III) and secondary antiphospholipid syndrome in October 1994. In December 2001 she was admitted for surgical drainage of a left salpingo-ovary abscess. She was on prednisolone (4 mg/day), hydroxychloroquine (400 mg/day) and acetylsalicylic acid (100 mg/day). On the fourth postoperative day she developed left common femoral vein thrombosis. On the ninth postoperative day the patient abruptly became dyspnoeic. The ECG showed inverted T waves in various leads. Serum troponin and CPK were within the normal range. Echocardiography revealed a depressed LVEF (30%) with diffuse hypokinesia and mild mitral valve regurgitation, but no evidence of myocardial infarction or pulmonary embolism. On the basis of these findings lupus myocarditis was diagnosed. No evidence of active nephritis was found. She was treated with intravenous methylprednisolone pulses (1 g on three sequential days) and an intravenous pulse of cyclophosphamide (1300 mg, 750 mg/m²) once a month for seven months, from December 2001 until June 2002. Her symptoms improved dramatically. Follow-up echocardiography in March 2002 and March 2008

showed an LVEF of 55 and 45%, respectively. She has been in remission ever since with a last follow-up in March 2008.

DISCUSSION

We describe six patients with severe heart failure due to SLE (summarised in *table 1*). Echocardiography was essential in confirming the clinical diagnosis of myocarditis and monitoring its activity over time, and excluding other causes of heart failure. Patient 1 also had significant pericardial effusion, but drainage did not result in improvement of heart failure. Five patients had evidence of lupus nephritis and a good response to immunosuppressive therapy with (methyl)prednisolone and cyclophosphamide. One patient was also treated with intravenous immunoglobulins; the contribution of this adjunct therapy to recovery was not clear. Cardiac function recovered in all patients within six months and remained normal over a mean follow-up period of 77 months. To our knowledge the present study is the first to describe clinical and echocardiographic data of cardiac function in this context with a long follow-up.

Various case reports demonstrated that severe myocardial dysfunction may potentially be reversible in SLE patients (*table 2*). Glucocorticoids are commonly used. Treatment with both glucocorticoids and cyclophosphamide has been reported to be superior to glucocorticoids alone, although controlled clinical trials to support this are lacking.¹¹⁻¹⁴ Severe myocarditis as a presentation of SLE is rare. Several authors described patients who presented with severe heart failure as initial presentation without classical clinical stigmata of lupus, similar to some of the patients in the present report.¹⁵⁻¹⁸ Busteed *et al.* reported on a patient who experienced a remission of myocarditis after treatment with methylprednisolone and six pulses of cyclophosphamide, but died 14 months later of lupus nephritis and cerebral vasculitis.¹³ The authors suggested that myocarditis carries a poor prognosis despite initial clinical remission. Disla *et al.* described a patient who was treated with intravenous immunoglobulins as well, because after pulse treatment with methylprednisolone 2 g and cyclophosphamide 500 mg/m² she still needed maximum doses of inotropic therapy and IABP was installed.¹⁹ Following treatment, full recovery was observed. In a few patients (patient 1, 2, 3, 6, and 14, *table 2*) histological evidence of lupus myocarditis was obtained. Endomyocardial biopsy is generally recommended in unexplained heart failure but can be complicated in critically ill patients by (fatal) rhythm disturbances.⁹ A negative biopsy does not rule out myocarditis and sensitivity and specificity are unknown. MRI has not yet been systematically evaluated in lupus patients with heart disease, although a preliminary report did reveal cardiac

Table 1. Characteristics of patients in present study

| Patient no. Age/sex | Disease duration | SLE manifestations before onset of heart involvement | Antibodies | LVEF (%) pre/post therapy | Nephritis yes/no | CPK | Therapy | Outcome | Follow-up (months) |
|------------------------|---------------------|---|--|---------------------------------|---------------------|-----|--|-------------|-----------------------|
| 1. 19/F | 1 month | Pancytopenia, fever | ANA+ Anti- dsDNA+ Anti-Sm+ Anti-CL+ | 25/50 | Yes | N | MP pulse CYC pulse IVIg | Improvement | 47 |
| 2. 37/F | 11 years | Polyarthriti- | ANA+ Anti- dsDNA- Anti-SSA- SSB- Anti-CL+ | 27/42 | Yes | N | Prednisolone 60 mg CYC pulse | Improvement | 90 |
| 3. 40/F | 0 year | None | ANA+ Anti- dsDNA+ Anti-PL+ Anti-CL+ | 23/63 | Yes | N | MP pulse AZA CYC pulse | Improvement | 92 |
| 4. 22/F | 4 months | Fever, polyarthri- tis, skin lesions, leukopenia | ANA+ Anti- dsDNA- Anti-SSA+ | 25/51 | Yes | ↑ | Prednisolone 60 mg AZA CYC pulse | Improvement | 113 |
| 5. 38/F | 1.5 year | Photosensitivity, malar rash, arthritis, oral ulcers, Raynauds | ANA- Anti- dsDNA- Anti-CL- | 37/60 | No | NA | MP pulse AZA HCQ | Improvement | 43 |
| 6. 37/F | 7.5 years | Photosensitivity, malar rash, arthritis, chorea | ANA+ Anti- dsDNA+ Anti-CL+ | 30/45 | No | N | MP pulse CYC pulse | Improvement | 75 |

MP = methylprednisolone; CYC = cyclophosphamide; IVIg = intravenous immunoglobulins; AZA = azathioprine; HCQ = hydroxychloroquine; NA = not available, N = normal, ↑ = increased.

abnormalities in patients with active disease.²⁰ Serum CPK levels were normal, except in patient 13 who was successfully resuscitated, patient 17 had mild elevation of CPK and troponin I (326 IU and 5.6 µg/l respectively, normal <160 IU and <0.2 µg/l) while having a flare of SLE myocarditis. In this patient cardiac catheterisation revealed normal coronary arteries.

Of note, five out of the six patients in our series had detectable anticardiolipin and/or antiphospholipid antibodies. It is unclear whether these antibodies are just a marker of underlying disease activity, are involved in the development of heart failure in lupus patients, or contribute to secondary intracavitary thrombus formation.²¹⁻²³ A recent large registry study involving 200 SLE patients, 42 of whom tested positive for antiphospholipid antibodies, showed an association with mitral valve nodules and mitral regurgitation but no association with other vascular abnormalities including systolic dysfunction.²⁴

The differential diagnosis of heart failure due to lupus myocarditis includes viral myocarditis related to the use of immunosuppressive drugs, ischaemic heart disease, and toxic myocarditis related to the use of antimalarial drugs. Severe cardiotoxicity may develop following prolonged use of antimalarials with both conduction disturbances

and congestive heart failure.²⁵ These cardiotoxic effects have been reported with chloroquine and less frequently with hydrochloroquine use alone. Clinical and echocardiographic presentations of antimalarial-induced cardiomyopathy often include a restrictive pattern and biventricular hypertrophy that can mimic amyloidosis.

CONCLUSION

Heart failure due to myocarditis can be the presenting (cardiac) manifestation of SLE, which requires prompt action. Echocardiography is an essential diagnostic tool. We report on six patients with a good clinical response on immunosuppressive therapy with a relatively long follow-up, including echocardiography. In our opinion therapy with pulses of methylprednisolone and intravenous cyclophosphamide is the therapy of choice given its rapid mode of action. Therapy should be started without delay. High-dose glucocorticoids plus an initial cycle of six monthly pulses of cyclophosphamide 750 mg/m², followed by a repeat cycle if LVEF has not completely normalised, is relatively well tolerated and effective. In our patients heart failure did not recur after successful treatment.

Table 2. Characteristics of patients in case reports

| Patient no. Age/sex | Disease duration | SLE manifestations before onset of heart involvement | Antibodies | LVEF (%) pre/post therapy | Nephritis yes/no | CPK | Therapy | Outcome | Ref. |
|---------------------|------------------|--|--------------------------------------|-----------------------------|------------------|-----|--|---|------|
| 1. 34/F | 2 years | NA | ANA+Anti-dsDNA+ | NA | NA | NA | Prednisolone 40 mg CYC 100 mg p.o. | Improvement | 27 |
| 2. 33/F | NA | NA | ANA+Anti-dsDNA- | NA | Yes | NA | Prednisolone 80 mg AZA | Improvement | 27 |
| 3. 62/F | 15 years | NA | NA | 10/NA | NA | NA | Prednisolone 60 mg | Improvement | 27 |
| 4. 46/F | 0 months | Lymphopenia, anaemia, fever | ANA+Anti-dsDNA- Anti-SSA+ | NA | No | NA | MP 80 mg i.v. | Recovery cardiac function (follow-up 1.5 years) | 15 |
| 5. 28/F | 1 years | Arthritis, fever, lymphopenia, lymphadenopathy | ANA+Anti-dsDNA+ Anti-Sm+ | NA | NA | NA | MP pulse CYC pulse IVIg | Functional recovery | 19 |
| 6. 38/M | 0 months | Oral ulcers, haemolytic anaemia | ANA+Anti-dsDNA+ | 45/65 | No | N | Prednisolone 1 mg/kg | Resolution of myocardial damage | 16 |
| 7. 30/F | 6 months | Rash, alopecia, arthritis, pleuritis, oral ulcers | ANA+Anti-dsDNA- | 34/55 | No | N | MP pulse AZA | Recovery cardiac function | 11 |
| 8. 55/M | 6 months | Proximal weakness, arthritis | ANA+Anti-dsDNA+ | 19/25 | No | N | AZA, (prednisolone 40 mg) | Improvement | 11 |
| 9. 20/F | 1 years | Vasculitis, pericarditis, arthritis | ANA+Anti-dsDNA+ | 20/46 | No | N | CYC pulse (prednisolone 80 mg) | Improvement | 11 |
| 10. 32/F | 2 years | Rash, arthritis, pleuritis, oral ulcers, nephritis | Anti-dsDNA+ | 20/45 | Yes | N | MP pulse CYC pulse | Improvement | 11 |
| 11. 45/F | 10 years | Rash, arthritis, vasculitis, interstitial lung disease | NA | 11/38 | No | N | Prednisolone 60 mg CYC pulse | Improvement | 11 |
| 12. 48/F | 3 years | Alopecia, arthritis, rash, photosensitivity | ANA+ | 11/30 | No | N | MP pulse CYC pulse | Improvement | 11 |
| 13. 59/F | Several years | Arthritis, pleuritis, sec. myelofibrosis | ANA+Anti-dsDNA- | 20/50 | NA | ↑* | IVIg (prednisolone 40 mg) | Recovery cardiac function | 28 |
| 14. 20/F | 3 years | Discoid rash, oral ulcers, seizure, myositis, leucopenia | ANA+ Anti-dsDNA+ Anti-SSA+ | 19/63 | Yes | N | CYC pulse Prednisolone 50 mg | Recovery myocarditis, nephritis no complete remission (follow-up 2 years) | 12 |
| 15. 23/F | 7 years | Malar rash, arthralgia | ANA+Anti-dsDNA+ | 40/55 | No | N | MP pulse CYC pulse | Recovery myocarditis death: nephritis, cerebral vasculitis(after 14 m) | 13 |
| 16. 43/F | 1.5 years | Raynaud, arthritis, myositis | ANA+Anti-dsDNA- Anti-RNP+Anti-Sm+ | 29/34 | No | N | Prednisolone 20 mg | Only mild improvement after 1 year | 29 |
| 17. 15/F | 1 years | Arthritis | ANA+Anti-dsDNA+ | 30/50 | No | N | MP pulse, MP pulse IVIg [†] | Marked improvement | 29 |
| 18. 22/M | 4 years | Autoimmune thrombopenia arthritis, nephritis | Anti-dsDNA+Anti-RNP+ | 40/55 [‡] 24/53 | Yes | ↑ | MP pulse CYC pulse [‡] | Improvement | 29 |
| 19. 36/F | 0 months | Serositis | ANA+Anti-dsDNA+ | 35/46 | Yes | N | MP pulse | Functional recovery | 17 |
| 20. 16/F | 0 months | Serositis, lymphopenia, nephritis | Anti-dsDNA+ | 28/NA | Yes | N | MP pulse | Recovery cardiac function renal: haemodialysis | 18 |
| 21. 45/M | NA | Photodermatitis, nephritis | ANF+Anti-dsDNA+ Anti-Sm+ | 27/NA | Yes | N | CYC pulse Prednisolone, HCQ | Recovery cardiac function | 14 |

*After resuscitation; †treatment for bicytopenia; ‡treatment for lupus nephritis; §recurrence of severe myocarditis in same patient after 6 years. MP = methylprednisolone; CYC = cyclophosphamide; IVIg = intravenous immunoglobulins; AZA = azathioprine; HCQ = hydroxychloroquine; NA = not available; N = normal. ↑ = increased.

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