Multifactorial aggressive and reversible cardiomyopathy in systemic lupus erythematosus

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Introduction

Patients with systemic lupus erythematosus have an inherent risk of developing heart failure as a result of premature epicardial coronary disease and lupus-associated myocarditis. This article describes the case of a 43-year-old woman in whom the risk of cardiomyopathy was amplified with immunosuppressive and antimalarial drug therapy for unremitting disease. Cardiac performance was restored after appropriate pharmacological justification and early treatment targeted at myocardial function. Furthermore, there was a parallel improvement in systemic disease with prednisolone monotherapy only. The potential adverse effect of polypharmacy in the development of heart failure in this population is underscored.

Case report

A 43-year-old Asian woman presented with acute heart failure 4 weeks after starting treatment with rituximab. She had been diagnosed with systemic lupus erythematosus 2 years previously, and with histologically proven lupus nephritis class III for the last year. During the first year there had been a good response with variable dose prednisolone, hydroxychloroquine 400 mg daily and intermittent periods of mycophenolate mofetil therapy 2 g daily.

Over the next 6 months, there was a steady decline in renal function, with the serum creatinine level climbing from baseline of 60 mmol/litre to 95 mmol/litre, alongside a rise in urine protein/creatinine ratio from 70 to 670 (urine protein/creatinine ratio of 100 equates approximately to 1 g proteinuria per 24 hours). Mycophenolate mofetil was withheld and despite six pulses of 1 g intravenous cyclophosphamide every 2–3 weeks (vasculitis protocol), there was little global systemic remission. Persistently elevated antibody to double-stranded deoxyribonucleic acid (anti-dsDNA) titre at >200 IU/ml and depleted complement factors C3 0.55 g/litre (normal range 0.75–1.65 g/litre) and C4 0.13 g/litre (normal range 0.20–0.65 g/litre) supported ongoing classical pathway activation and immune complex disease. B-cell depletion therapy with rituximab was initiated, alongside prednisolone and hydroxychloroquine.

Four weeks after the second infusion of rituximab (the protocol being two initial doses of 1 g 2 weeks apart, followed by 1 g 6-monthly), she presented in biventricular failure requiring intubation, ventilation and inotropic support. Transthoracic echocardiography demonstrated severe left ventricular dilatation, global hypokinesia and ejection fraction at 23%. Laboratory investigations were notable for estimated glomerular filtration rate of 47 ml/min/1.73 m^2 and anti-dsDNA titre >200 IU/ml with reduced C3 but now normal C4 levels (suggesting an alternative pathway and nephritic factor activity). The plasma level of N-terminal pro B-type natriuretic peptide (NT-proBNP) was elevated at 5706 pg/ml (normal <125 pg/ml). The patient responded well to diuresis and respiratory weaning, with bilevel positive airway pressure allowing stepdown to the coronary care unit after 72 hours.

Cardiac magnetic resonance imaging demonstrated patchy, diffuse replacement fibrosis involving left ventricular mid-wall, basal septal wall, extending to the mid-apical septum in a non-coronary artery distribution and there was absent late gadolinium enhancement. The cardiac valves and pericardium were unaffected (Figure 1). These findings were in keeping with non-ischaemic cardiomyopathy, potentially attributable to medication exposure. Hereafter, the patient was treated with a single 250 mg dose of pulsed intravenous methylprednisolone and a tapering regimen of prednisolone monotherapy for systemic lupus erythematosus (40 mg for 1 week, decreased to 30 mg for 2 weeks and then decreased by 5 mg every 2 weeks down to 20 mg, and then decreased by 2.5 mg every 2 weeks to a maintenance dose of 10 mg).

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Case report (Continued)

At follow up 2 months later, and now established on anti-heart failure pharmacotherapy (ramipril 5 mg, spironolactone 25 mg, nebivolol 2.5 mg and furosemide 40 mg daily), symptoms and signs of heart failure had resolved, and there were no features of active lupus. On transthoracic echocardiography, left ventricular dimensions were normal, and function had improved with ejection fraction 38%. A drop in plasma NT-proBNP to 2277 pg/ml implied that there was ongoing positive myocardial remodelling, and supported a diagnosis of drug-induced cardiomyopathy with reversibility. At 12-month follow up, the patient had no signs of volume overload, and transthoracic echocardiography demonstrated normal cardiac structure and function. On further follow up at 18 months, she had been reviewed at a tertiary referral centre for lupus and, on their advice, received a single low dose rituximab 500 mg infusion with repeat at 6 months planned. There were no signs of heart failure, and she continued on targeted cardiac pharmacotherapy, prednisolone (currently 5 mg), in addition to a cautious reintroduction of hydroxychloroquine at a reduced dose of 200 mg once daily and tacrolimus 2 mg twice daily for lupus nephritis, with stable renal and systemic disease.

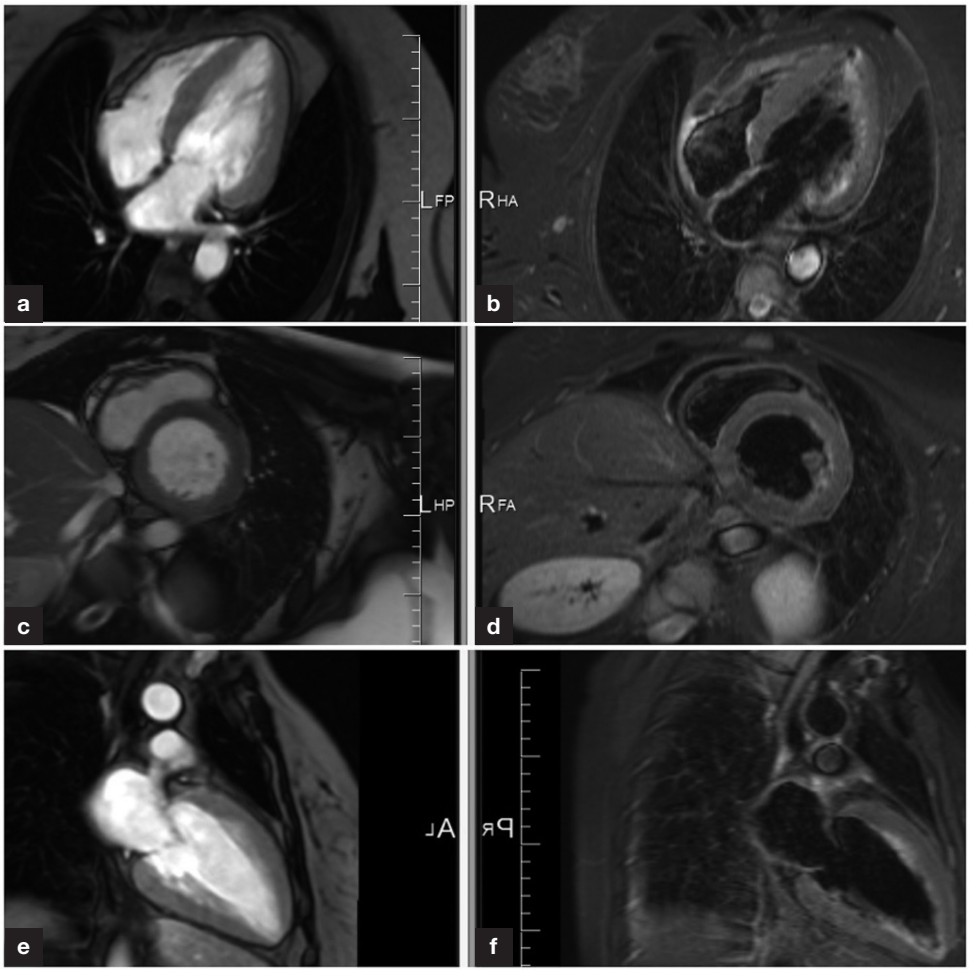

Figure 1. Cardiac magnetic resonance imaging in (a,b) transverse, (c,d) coronal and (e,f) sagittal planes demonstrating (b,d,f) diffuse and patchy ventricular wall thickening with absent late gadolinium enhancement.

Discussion

Systemic lupus erythematosus complicated by heart failure is potentially multifactorial. The differential diagnosis includes myocardial microvascular dysfunction resulting from chronic inflammation (Chen et al, 2019) ('lupus myocarditis'), accelerated coronary

Learning points

- Systemic lupus erythematosus complicated by heart failure is potentially multifactorial.
- The risk of developing heart failure is related to myocarditis from chronic inflammation, accelerated coronary atheromatous disease and pulmonary hypertension consequent to pulmonary thromboembolic and parenchymatous disease.
- Treatment with immunosuppressive and antimalarial drugs, independently or together, increases the risk of developing heart failure.
- The mainstay of the management of heart failure in these patients is anti-heart failure medical therapy, and rationalisation of immunosuppressive and antimalarial therapies.
- High-dose steroids with a tapering regimen is an alternative first line of therapy in patients with suspected drug-induced cardiomyopathy.

atheromatous disease (ischaemic cardiomyopathy) (Torres et al, 2009), and cardiomyopathy related to immunosuppressive and antimalarial drugs. In addition, many intrapulmonary complications of systemic lupus erythematosus, such as thrombosis (particularly in the presence of antiphospholipid antibodies), vasculitis, endothelial dysfunction-mediated vasoconstriction and interstitial fibrosis are implicated in the development of pulmonary artery hypertension and right ventricular failure (Tselios et al, 2016). These aetiologies, independently or together, increase the risk of heart disease in this patient group.

Clinical, echocardiographic and cardiac magnetic resonance imaging features of antimalarial-induced cardiomyopathy follow a restrictive pattern with ventricular hypertrophy that mimics amyloidosis (Joyce et al, 2013), which was not seen in this case. Cyclophosphamide-induced cardiotoxicity is characterised by acute heart failure developing within 48 hours to 10 days from initiation (Dhesi et al, 2013). Lupus myocarditis presents as pancarditis (oedema rather than fibrosis) with pericardial and valvular involvement and positive late gadolinium enhancement on cardiac magnetic resonance imaging (Barillas, 2016); features again not seen in this case. Late gadolinium enhancement is also present in idiopathic dilated cardiomyopathy.

In the absence of patterns associated with ischaemic cardiomyopathy, lupus myocarditis or dilated cardiomyopathy on cardiac magnetic resonance imaging, the cumulative toxicity of rituximab may have caused myocardial dysfunction, and concomitant treatment with hydroxychloroquine and cyclophosphamide may have augmented the risk of heart failure in this patient.

Conclusions

Heart failure in patients with systemic lupus erythematosus may have multiple possible pathological processes. Emphasis is therefore laid upon the potential synergistic adverse effect of polypharmacy in the development of toxic or accelerated lupus-related cardiomyopathy. Rationalisation of pharmacotherapy and early targeted treatment can restore myocardial function.

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References

Barillas M. Viral myocarditis vs lupus myocarditis, distinctive features in cardiovascular magnetic resonance. J Cardiovasc Magn Reson. 2016;18(S1):O97. https://doi.org/10.1186/1532-429X-18-S1-O97

Chen SK, Barbhaiya M, Fischer M et al. Heart failure risk in systemic lupus erythematosus compared to diabetes mellitus and general medicaid patients. Semin Arthritis Rheum. 2019; 49(3):389–395. https://doi.org/10.1016/j.semarthrit.2019.06.005

Dhesi S, Chu MP, Blevins G et al. Cyclophosphamide-induced cardiomyopathy: a case report, review, and recommendations for management. J Investig Med High Impact Case Rep. 2013;1(1):2324709613480346. https://doi.org/10.1177/2324709613480346

Joyce E, Fabre A, Mahon N. Hydroxychloroquine cardiotoxicity presenting as a rapidly evolving biventricular cardiomyopathy: key diagnostic features and literature review. Eur Heart J Acute Cardiovasc Care. 2013;2(1):77–83. https://doi.org/10.1177/2048872612471215

Torres A, Askari AD, Malemud CJ. Cardiovascular disease complications in systemic lupus erethymatosous. Biomark Med. 2009;3(3):239–252. https://doi.org/10.2217/bmm.09.14

Tselios K, Gladman DD, Urowitz MB. Systemic lupus erythematosus and pulmonary arterial hypertension: links, risks, and management strategies. Open Access Rheumatol. 2016;9:1–9. https://doi.org/10.2147/OARRR.S123549