

Difficult Lupus: A Heart-wrenching Case

By Stephanie Keeling, MD, MSc, FRCPC

Case: A previously well 31-year-old Vietnamese female, who moved to Canada ten years ago (G2TA1), delivered a healthy son at 41+ three days in October 2016 by cesarean section after failing to progress despite oxytocin augmentation. Her pregnancy was uneventful other than group B streptococcal positivity requiring penicillin predelivery. She had an older sister with systemic lupus erythematosus (SLE) and was on L-thyroxine for hypothyroidism.

Two months postpartum, she presented to her family doctor with sore throat and slight facial rash treated with amoxicillin. Due to worsening of her symptoms, she presented two days later to a local community hospital. She received supportive care (acetaminophen and dimenhydrinate) and was discharged with a diagnosis of an influenza-like illness. She returned several days later with increased cough, high fever, worsening facial rash, myalgias, and arthralgias. She was admitted for presumed pneumonia, worsening leg edema and treated with intravenous ceftriaxone, although pancultures were negative. Despite discharge, she presented several days later to the University Hospital in biventricular failure (Brain Natriuretic Peptide (BNP) > 3000 [very high]) and was admitted to the coronary care unit (CCU) for therapy with milrinone, bilevel positive airway pressure (BiPAP) support, blood transfusion and close monitoring by the cardiac transplant team.

Rheumatology and nephrology were consulted due to suspicion of SLE based on her acutely worsening malar rash and labs, including worsening renal function with active urinary sediment. She was anti-nuclear antibody (ANA) positive, extractable nuclear antigen (ENA) negative, strongly positive for double-stranded DNA, significantly hypocomplementemic (C3/C4), pancytopenic (hemoglobin 83 g/L, platelets 92,000 per mL, white blood cells $1.0 \times 10^9/L$ with $0.5 \times 10^9/L$ neutrophils). Antiphospholipid antibodies (*i.e.*, anticardiolipin and lupus anticoagulant) were negative. A renal biopsy showed diffuse proliferative nephritis (Class 4). Echocardiogram showed left ventricular ejection fraction [EF] of 10-15%.

In addition to supportive therapies for her profound heart failure, she received 1 g methylprednisolone pulse daily for three days, followed by prednisone 1 mg/kg/day. After lengthy discussions between multiple specialists debating between cyclophosphamide and mycophenolate mofetil (MMF), MMF was initially prescribed at 1000 mg twice a day (targeted dose of 1500 mg bid; patient weight 50 kg) in addition to hydroxychloroquine 300 mg daily. Due to initial poor response of her cardiac status and concern that her cardiomyopathy was related to her acute new presentation of SLE, rituximab 1000 mg doses two weeks apart were added; the first dose was given within two weeks of presentation.

A cardiac magnetic resonance imaging (MRI) was performed approximately four weeks after her SLE therapies were initiated and showed no delayed gadolinium enhancement, infarct or infiltrates and no valvular abnormalities. She had a small anterior pericardial effusion, severely dilated left ventricle (EF 22%) with preserved right ventricle. The delay in obtaining cardiac imaging reflected the significant instability of the patient who remained too tachycardic and renally insufficient to perform the test earlier.

Despite a hospital course complicated by profound suicidal ideation (brain MRI normal), the patient stabilized over four weeks in hospital and a repeat echocardiogram showed improved left ventricle (LV) EF of 30-35%. Clinically, her heart failure symptoms markedly improved to a New York Heart Association (NYHA) Class II status post-discharge on carvedilol, ramipril, and spironolactone. Other than steroid side effects including moon facies, she had no persistent manifestations of lupus, including no acute or chronic cutaneous lupus, pancytopenia, or arthritis. Her renal function normalized with no active urinary sediment. Complement levels and double-stranded DNA also normalized.

The patient returned to her new business running a beauty salon within two weeks of discharge and continued to care for her four-month-old son. She had ongoing questions regarding her diagnosis, the need for long-term medications, as well as confusion about the etiology of her cardiac diagnosis, which was officially deemed to be post-partum cardiomyopathy by cardiology. In contrast, the multiple rheumatology consultants involved in her care attributed the cardiac manifestations to her active SLE.

This complex case of new-onset SLE in a young post-partum female presented many challenges for the multiple consultants and trainees involved in the case, all of which cannot be done justice in this Hallway Consult. These challenges included: a) attribution of the cardiac manifestations; b) urgent therapeutic interventions for active SLE including cardiac manifestations; c) etiology of her suicidal ideation; d) limitations in conducting the best cardiac evaluations during her CCU stay due to instability; e) lack of congruence between patient and physician expectations for prognosis and long-term medications; and f) communicating with the patient and other specialists when specific diagnoses were questioned.

Postpartum cardiomyopathy (PPCM) is diagnosed in women without past history of heart disease, within one month before delivery or up to five months postpartum, and can account for up to 11% of maternal deaths.¹ While full recovery is expected within six months of disease onset in approximately 50% of women, long-term sequelae include heart failure and death, and recurrence of PPCM can be seen in up to 50% of women in a subsequent pregnancy.¹ The etiology of PPCM is unclear but may include inflammation, autoimmune processes, apoptosis, viral infections, malnutrition, hormonal abnormalities, stress-activated cytokines and endothelial dysfunction.² Moreover, an important role of prolactin has been postulated whereby cathepsin D cleaves prolactin leading to oxidative stress on the endothelium, cardiac vasculature and cardiomyocyte function.^{3,4}

Cardiac disease in SLE encompasses the spectrum of coronary artery-related and non-coronary artery-related diseases. Specific non-coronary artery diseases include valvular vegetations (*e.g.*, Libman Sacks), antiphospholipid antibodies and valvular disease, pericardial disease, myocarditis and conduction abnormalities.^{5,6,7} Lupus myocarditis, cardiomyopathy and heart failure are uncommon in lupus.⁸ The prevalence of lupus myocarditis is discrepant between biopsy studies in autopsy studies compared to clinical diagnoses of myocarditis and findings in clinical series.⁹ Extrapolating to our patient, other factors rather than myocardial inflammation may have had a causal pathophysiologic role inducing a stress-like cardiomyopathy^{8,10,11}.

In the case of our patient, she received urgent interventions for cardiac failure and acute severe lupus at the same time. She was unable to have a myocardial biopsy due to her clinical instability, and was well into therapy and improved when she might have tolerated the procedure. The choice of MMF versus cyclophosphamide reflected the totality of her lupus manifestations, young age (although everyone agreed she should never pursue another pregnancy), and concerns voiced by several colleagues about the risk of cyclophosphamide inducing heart failure (albeit rare and arguably con-

troversial in this clinical situation). Evidence for treating SLE-related cardiomyopathy/myocarditis remains observational and largely based on case reports and case series.^{12,13}

Fortunately, our patient recovered within the expected window where her SLE medications including rituximab, MMF, and hydroxychloroquine would be expected to work and while also continuing on moderate prednisone doses and congestive heart failure medications. Her clinical resolution also fell into the expected time period where PPCM typically improves. While the attribution of her cardiac failure differed between rheumatology and cardiology, a unifying theory may be that the acute onset of SLE was enough of a stress-like state to trigger PPCM. However, the acuity of her presentation and knowledge that SLE can lead to significant cardiac failure are difficult to ignore.

Recognizing the serious morbidity and mortality of both PPCM and SLE-related cardiomyopathy, it is extremely fortunate that she is trending towards recovery at this time, given how guarded her prognosis was. Further monitoring of her heart function in conjunction with cardiology is planned, and assessments in lupus clinic continue. Critical pieces to her long-term prognosis include education on her medications – especially given the questions she asked on her most recent follow-up as she walked out the door: “When can I stop my hydroxychloroquine?” and “Are you sure I cannot get pregnant again?”

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Stephanie Keeling, MD, MSc, FRCPC
Associate Professor of Medicine, University of Alberta
Edmonton, Alberta