



# Cardiomyopathy following COVID-19 vaccination in a patient with systemic lupus erythematosus

Avreena Kaur Bhullar<sup>a,\*</sup>, Zhi Chee Chew<sup>a</sup>, Ping Seung Ong<sup>a</sup>, Chiew Gek Khor<sup>a</sup> and Nor Hanim Mohd Amin<sup>b</sup>

<sup>a</sup>Department of Medicine, Rheumatology Unit, Hospital Raja Permaisuri Bainun, Ipoh, Perak, Malaysia

<sup>b</sup>Department of Medicine, Cardiology Unit, Hospital Raja Permaisuri Bainun, Ipoh, Perak, Malaysia

\*Correspondence: Avreena Kaur Bhullar; [avreena@hotmail.com](mailto:avreena@hotmail.com); Department of Medicine, Rheumatology Unit, Hospital Raja Permaisuri Bainun, 10, Jalan Habib Abdullah, Taman Merdeka, Ipoh, Perak 30100, Malaysia.

## ABSTRACT

There are an increasing number of reports of myocarditis associated with mRNA-based COVID-19 vaccination. We describe the case of a female patient with underlying systemic lupus erythematosus, who developed heart failure symptoms following a second dose of the BNT162b2 vaccine. Despite her history of refractory systemic lupus erythematosus, the disease remained stable after she began rituximab treatment. She underwent serial transthoracic echocardiogram and cardiac magnetic resonance imaging for the evaluation of cardiomyopathy. She showed improvement in cardiac function after treatment with glucocorticoids and intravenous immunoglobulin therapy.

**KEYWORDS:** Systemic lupus erythematosus; cardiomyopathy; myocarditis; COVID-19; vaccination

## Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune inflammatory disease that can affect multiple organs including the heart. Myocarditis occurs in 5–10% of SLE patients, and postmortem studies suggest a higher prevalence of subclinical myocarditis [1]. Myocarditis is an inflammatory disease of the cardiac muscles. The symptoms of myocarditis vary from minor symptoms that do not require treatment to fulminant cardiac failure leading to death [2, 3]. Since the implementation of the global vaccination programme during the SARS-CoV-2 pandemic, cases of myocarditis and pericarditis have been reported post-mRNA-based COVID-19 vaccination.

## Case report

We present the case of a 42-year-old lady who was diagnosed with SLE in 2006. She initially presented with oral ulcers, discoid and photosensitive rash, alopecia, and arthritis. She also had nephrotic range proteinuria and pericardial effusion. Immunologically, her serum anti-nuclear antibodies were negative, anti-double stranded DNA (anti-dsDNA) antibodies were positive, with low complement levels. Renal biopsy revealed Class III–V lupus nephritis. She was treated with glucocorticoids and multiple immunosuppressants, including cyclophosphamide, mycophenolate mofetil, azathioprine, and cyclosporine A. She failed to achieve partial remission of her lupus nephritis and had multiple mucocutaneous and arthritis flares over the years. Clinical assessments and serial transthoracic echocardiogram (TTE) over her disease course did not

show evidence of myocarditis or impaired ventricular function. In view of her persistent disease activity, she was started on 6 monthly IV rituximab, administered at doses of 500 mg on days 1 and 15 since December 2020. The last cycle of rituximab was administered in June 2021.

She presented to a district hospital in October 2021 with chest discomfort, fever, orthopnoea, and reduced effort tolerance 4 days after receiving a second dose of the BNT162b2 vaccine. The patient was treated for viral infection and was subsequently discharged home. No inflammatory markers, cardiac enzymes, electrocardiography (ECG), or TTE were performed during hospitalization. She continued to experience reduced effort tolerance, New York Heart Association (NYHA) Class III, orthopnoea, and paroxysmal nocturnal dyspnoea since her hospitalization; however, she had no other symptoms suggestive of SLE flare.

During her routine follow-up at our rheumatology clinic 1 month later, she was admitted for further investigation because of her heart failure symptoms. She was afebrile and vital signs were within the normal range. Cardiovascular examination revealed a raised jugular venous pressure and a displaced apex beat, and heart sounds were normal with no pericardial rub.

Laboratory investigations revealed anaemia with haemoglobin of 9.2 g/dL, and the white blood cell and platelet counts were within the normal range. Her baseline haemoglobin level during follow-up ranged from 9 to 10 g/dL. Renal function was static, with urea of 13 mmol/L and creatinine 167 µmol/L. C-reactive protein was 25.3 mg/L (normal <5 mg/L). She had borderline low C3 at 0.73 g/L (normal 0.8–1.9), while C4 was normal. The NT proB-type

**Table 1.** Laboratory data, current therapy, and SLEDAI-2K in relation to rituximab.

Parameters (unit) (range)	December 2020 (first rituximab)	June 2021 (second rituximab)	November 2021 (current presentation)
White cell count ( $10^9/L$ ) (4.0–11.0)	3.5	9.8	7.4
Haemoglobin (g/dL) (11.5–16)	9.9	9.7	9.2
Platelet ( $10^9/L$ ) (150–400)	225	388	324
Absolute lymphocyte count ( $10^9/L$ ) (1.0–3.0)	0.54	2.6	1.9
Urine microscopy	Protein 4+, blood negative	Protein 2+, blood negative	Protein 3+, blood negative
24 hour urine protein	3.1 g/day	1.15 g/day	898 m/day
Serum creatinine ( $\mu\text{mol/L}$ ) (53–115)	161	181	167
C3/C4 (g/L) (0.8–1.9/0.1–0.4)	0.53/0.07	0.75/0.15	0.73/0.17
Anti-dsDNA (IU/ml) (positive >10)	30	NA	NA
Current therapy			
Prednisolone	10 mg OD	5 mg OD	5 mg OD
Mycophenolate mofetil	750 mg BD	1 g BD	1 g BD
Hydroxychloroquine	200 mg OD	200 mg OD	200 mg OD
SLEDAI-2K	16	6 <sup>a</sup>	Not applicable

Abbreviations: C3/C4: complement 3, complement 4; anti-dsDNA: anti double stranded DNA; NA: not available.

<sup>a</sup>No anti-dsDNA titre available.

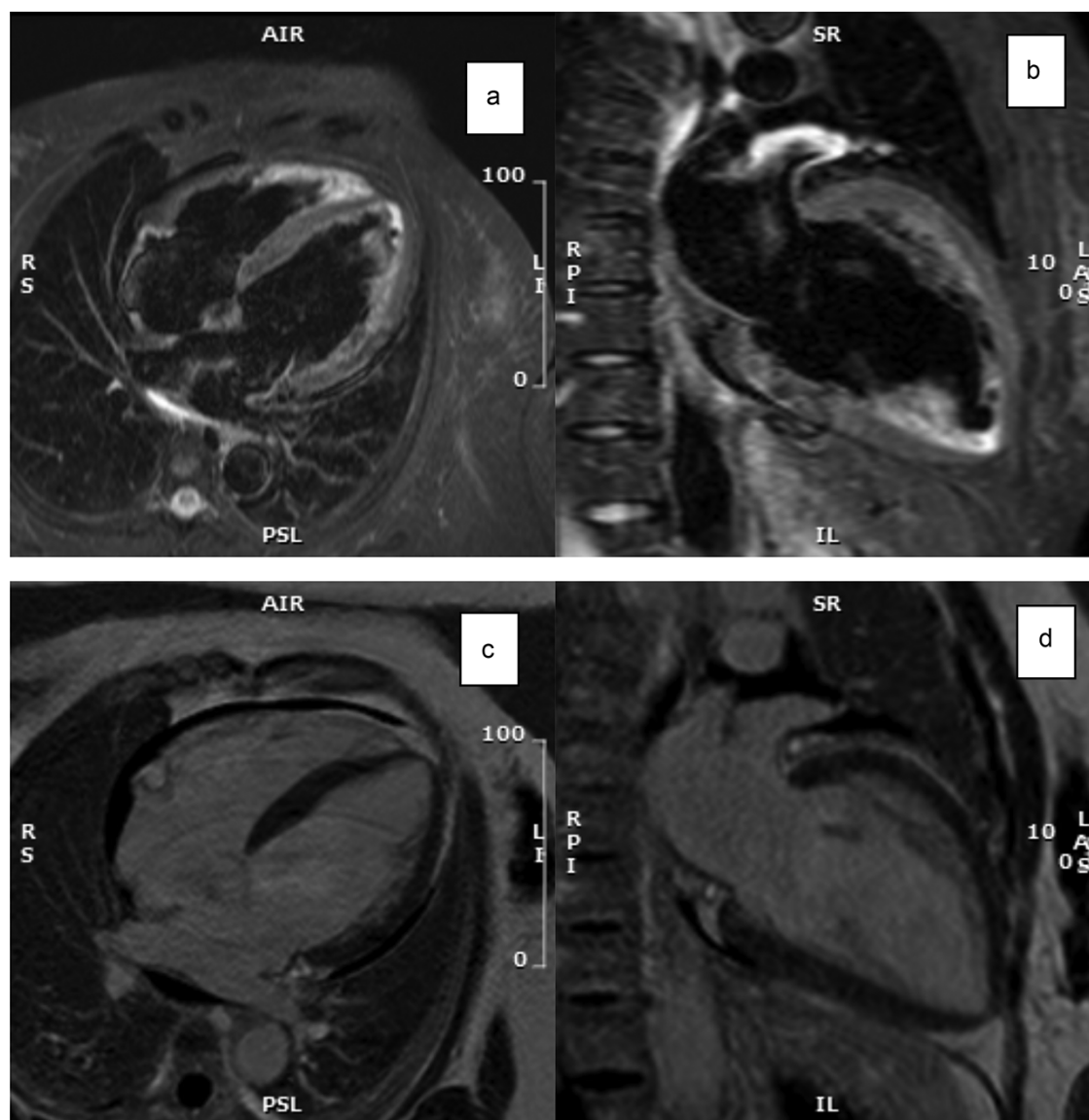


**Figure 1.** Transthoracic echocardiogram. (a) Normal baseline cardiac LV function in 2020. (b) LV dysfunction with EF 33.6% and global hypokinesia in October 2021. (c) Improvement of the EF 50.4% with no regional hypokinesia in November 2021. (d) LVEF of 49.5% in March 2022.

natriuretic peptide was elevated to 449 pg/mL (normal <300 pg/mL). The high-sensitivity cardiac troponin I was 5.2 ng/L (<15.9 ng/L) and creatine kinase was 40 U/L (29–168 U/L). The SARS-CoV-2 molecular swab was negative, whereas her SARS-CoV-2 antibodies (IgG antibodies to the RBD of the viral spike(S) protein) were positive. ECG showed no changes suggestive of ischemia or pericarditis,

whereas gross cardiomegaly was observed on chest radiography. The laboratory data, treatment, and SLEDAI-2K disease activity scores in relation to rituximab therapy are listed in [Table 1](#).

TTE ([Figure 1](#)) revealed significant left ventricular (LV) dysfunction with an ejection fraction (EF) of 33%, global hypokinesia, and global pericardial effusion. Her baseline



**Figure 2.** Cardiac MRI. T2STIR images (a and b) showed no evidence of acute myocardial injury or acute myocardial inflammation. (c and d) No evidence of myocardial fibrosis, myocardial infiltrative disease, or previous myocardial infarction. LGE, late gadolinium enhancement images.

TTE performed 1 year prior had good LV function with an EF of 63.5%.

As her symptoms arose after the second dose of COVID-19 vaccine, a diagnosis of cardiomyopathy following the BNT162b2 vaccine was made. Intravenous hydrocortisone 100 mg TDS and intravenous immunoglobulin 0.5 g/kg/day for 4 days were initiated. Her symptoms of failure improved upon completion of treatment. Repeated TTE after treatment revealed an improvement in LV function (EF 50.4%) with minimal inferior wall hypokinesia. Cardiac magnetic resonance (CMR) (Figure 2) performed 2 weeks later showed non-ischemic dilated cardiomyopathy with mild LV systolic dysfunction, a LV EF of 51% with the absence of myocardial oedema and no delayed enhancement indicating the absence of scarring or fibrosis. The patient was discharged with daily prednisolone 30 mg.

She was closely followed up with regular clinical evaluation and serial TTE. Her SLE remained stable and she had no recurrence of heart failure symptoms. Her prednisolone dose

was gradually tapered to 5 mg daily over 4 months and she was continued on a 6 monthly rituximab treatment. Recent TTE in March 2022 showed stable LV function. The case was reported to the Malaysian National Adverse Events Following Immunisation (AEFI) Registry.

## Discussion

In this young woman with a long-standing history of SLE, we considered multiple aetiologies for her new onset cardiomyopathy, including ischemic cardiomyopathy, flare of SLE, viral myocarditis, and perimyocarditis following mRNA-based COVID-19 vaccination.

The presence of traditional cardiovascular risk factors such as hypertension, dyslipidaemia, chronic kidney disease, and a long history of auto-immune inflammatory disease puts her at risk of ischemic cardiomyopathy. Cardiac MRI confirmed non-ischemic dilated cardiomyopathy.

Her SLE was stable after the initiation of rituximab therapy in 2020. She had complete resolution of the arthritis and discoid rash. She achieved partial remission of her lupus nephritis, with >50% reduction in proteinuria and stable creatinine levels. Her C3 level, albeit low during this presentation, was similar to her baseline C3 level over the past 6 months. Her prednisolone dose was successfully tapered to 5 mg daily, with no recent dose increment. Anti-dsDNA titres were not routinely monitored because of cost constraints. Reports suggest that most patients who developed post-vaccine exacerbation of disease activity, had only mild flares of short duration, predominantly musculoskeletal, and skin manifestation [4, 5]. Thus, it is unlikely that her cardiomyopathy was due to the exacerbation of SLE disease activity in the absence of other signs and symptoms of active disease, namely arthritis and rashes which were the main manifestations in the past.

The Siemens Atellica Chemiluminescent Immunoassay was used for the quantitative determination of IgG antibodies to the RBD of the viral spike(S) protein, of which the patient had positive results of 3.11 U/mL ( $\geq 1.0$  U/mL was considered positive), measured 5 weeks after the second dose of BNT162b2 vaccine. With no history of previous COVID-19 infection, this supports the hypothesis that humoral immunity was induced by BNT162b2 vaccine despite administration of the vaccine 4 months after rituximab therapy. A study by Bonelli *et al.* [6] suggested that vaccination can induce SARS-CoV-2 specific antibodies in rituximab-treated patients once peripheral B cells are at least partially repopulated. Similar data were reported in other studies, where a longer duration from rituximab exposure, as well as B-cell reconstitution, was associated with a greater likelihood of humoral response [7]. In our resource-limited setting, flow cytometry to assess B-cell depletion is not routinely performed for patients undergoing B-cell depletion therapy.

Rituximab therapy has individual variability in terms of clinical response. It can be hypothesized that our patient had incomplete B cell depletion, however, still able to mount a good clinical response in terms of controlling her SLE disease activity. The incomplete B-cell depletion explains her ability to mount a humoral antibody response to the vaccine. Our patient, with body surface area of 1.64 m<sup>2</sup>, received two doses of IV rituximab 500 mg every 6 months, which could be insufficient to achieve complete B-cell depletion. Factors that have been described to influence incomplete B-cell depletion include insufficient dose, increased clearance, and resistance of B-cell clones to depletion mechanisms [8].

The strong temporal relationship of her symptoms, which began shortly after receiving the vaccine supports the diagnosis of cardiomyopathy secondary to the COVID-19 vaccine, possibly a sequela of vaccine-related perimyocarditis. Unfortunately, we did not have conclusive evidence of myocarditis during her initial hospitalization as thorough investigations were not performed.

Patients with previous myocarditis may present with non-ischemic dilated cardiomyopathy after a few weeks of undiagnosed symptoms. These symptoms may vary from reduced effort tolerance to fulminant cardiac dysfunction in cardiogenic shock and arrhythmias [9, 10]. Diagnostic tools for myocarditis include laboratory testing for serum C-reactive protein, cardiac enzymes, and BNP. However, normal cardiac

troponin or creatine kinase myocardial-band values do not exclude the presence of myocarditis [9]. The American Heart Association recommends imaging modalities such as TTE and CMR for the evaluation of myocarditis [10]. The percentage of patients with TTE abnormalities following COVID-19 mRNA-vaccine myocarditis was highly variable in case reports, while CMR findings suggestive of myocarditis, such as myocardial oedema and late gadolinium enhancement were observed in the majority of patients [11].

Since the implementation of the global COVID-19 vaccination program, there have been reports of acute perimyocarditis with significant temporal links to vaccination [12–15]. Although myocarditis is a rare adverse event following vaccination, there have been documented cases associated with certain vaccines, such as the smallpox vaccine [16]. Data from adolescent studies suggest that symptoms due to myopericarditis after the mRNA-based COVID-19 vaccination tend to be mild and transient [17].

From published case reports, non-steroidal anti-inflammatory drugs, colchicine, and steroids have been used for treatment of vaccine induced myocarditis in addition to standard supportive care. Although there are no prospective or randomized controlled trials, it is reasonable to consider intravenous immunoglobulins in patients with significant symptoms and evidence of severe LV dysfunction [11].

## Conclusion

Management of non-ischemic cardiomyopathy in patients with autoimmune disease is challenging owing to multiple possible aetiologies, limitations in diagnostic tools, and evidence on treatment strategies. In this complex case of a new-onset cardiomyopathy following the BNT162b2 vaccine, with a background history of refractory SLE on rituximab therapy, we highlight our approach to diagnosis, treatment, and patient outcome. Cardiomyopathy as a possible sequela of perimyocarditis following vaccination is a rare complication of mRNA-based COVID-19 vaccination and this should not diminish confidence in the importance of vaccination especially among patients with rheumatic and musculoskeletal diseases.

## Conflict of interest

None declared.

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## Patient consent

The patient signed a written informed consent prior to her inclusion in the report.

## Ethical approval

Not applicable.



## Author contributions

Avreena Kaur Bhullar and Chew Zhi Chee contributed to writing of the manuscript, while Ong Ping Seung, Khor Chiew Gek, and Nor Hanim Mohd Amin supervised the work.

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