Acute Myocarditis in Patients with Antineutrophil Cytoplasmic Antibody–positive Microscopic Polyangiitis and Receiving Rituximab Therapy

To the Editor:

The presence of cardiac insufficiency is recognized as a poor prognostic factor in antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV)[1], and heart failure is an identified mortality risk factor for eosinophilic granulomatosis with polyangiitis (EGPA)[2]. Microscopic polyangiitis (MPA) has lower frequencies of myocardial involvement with rarely reported acute myocarditis presentation[3]. Rituximab (RTX) is a first-line induction therapy licensed for severe MPA with reduced ANCA titers and clinical remission[4]. In this study, we reviewed hospitalized patients with MPA who were receiving RTX therapy for acute myocarditis-related heart failure.

A retrospective study was carried out at the National Cheng Kung University Hospital from January 2014 to December 2018. Hospitalized patients fulfilling the 2012 Revised Chapel Hill Consensus Conference MPA definition[5] were analyzed under the permission of the institutional review board (approval no. B-ER-105-108). Acute myocarditis was defined as (1) symptoms such as fever, dyspnea, orthopnea, chest pain, and palpitation; (2) raised cardiac biomarker levels; and (3) new/worsening echocardiograph or cardiac magnetic resonance imaging (cMRI) changes including wall motion abnormalities and impaired left ventricular ejection fraction (LVEF)[6,7], excluding myocardial dysfunction attributed to coronary artery disease and viral myocarditis. Data were expressed as mean and SD.

Ten patients fulfilled the MPA definition, with 5 males aged 34–78 years (60.2 ± 14.6). At disease onset, all had myeloperoxidase (MPO) antibody, and Birmingham Vasculitis Activity Score (BVAS)[8] 17 to 39 (26 ± 6) and 5-factor score (FFS)[1] 1 to 3 (1.9 ± 0.7). Medications and procedures included corticosteroid (CS) or plus pulse methylprednisolone, cyclophosphamide (CYC), RTX, and plasma exchange for induction therapy, and CS and azathioprine (AZA) for maintenance treatment.

Three males had acute myocarditis. They were aged 53 to 82 years (66.3 ± 14.6), and all had acute myocarditis as a later development, 1 to 13 years (7.3 ± 6.0) after the disease onset (Table 1). BVAS was 26 to 30 (28 ± 2) and FFS 2 or 3 (2.7 ± 0.6). In addition to proteinuria and microscopic hematuria, cases 1 and 2 had impaired estimated glomerular filtration rate (eGFR). All had parenchymal lung involvement, with diffuse alveolar hemorrhage (DAH) in case 1.

There were myocarditis-related symptoms with New York Heart Association Functional Classification (NYHAFC) II to IV and elevated anti-MPO and cardiac troponin I levels before the RTX therapy. The medications before prescribing RTX were CYC and CS for induction in case 1. Cases 2 and 3 received initial induction with CYC and CS at the disease diagnosis, followed by AZA and CS maintenance. The indications for RTX were refractory disease in case 1 and relapse activity in cases 2 and 3 with a regimen of 375 mg/m^2 weekly × 4, resulting in a complete B cell depletion (0/μl). In addition to absent anti-MPO and lower BVAS (7.0 ± 2.6), all had decreased NYHAFC to I after the RTX therapy. Besides LV enlargement, there were global hypokinesia/impaired LVEF in echocardiograph before the usage, and normalized LVEF without chamber enlargement/hypokinesia after the therapy. The cMRI revealed myocarditis-related late gadolinium

Table 1. Clinical/medication data of MPA myocarditis before and after RTX therapy.

Characteristics	Case 1	Case 2	Case 3
Age, yrs*/sex	53/male	82/male	64/male
Presentation after onset	8 yrs later	13 yrs later	1 yr later
Anti-MPO before/after	51.7 IU/ml/ND	49.5 IU/ml/ND	70.3 IU/ml/ND
BVAS before/after	30/10	26/5	28/6
FFS	3	3	2
Renal findings	Impaired eGFR, proteinuria, hematuria	Impaired eGFR, proteinuria, hematuria	Proteinuria, hematuria
Pulmonary findings	DAH, PLI	PLI	PLI
Myocarditis symptoms	Fever, chest pain, dyspnea, orthopnea, palpitation	Fever, dyspnea, orthopnea, palpitation	Fever, chest pain, dyspnea
Pedal edema	Nil (under dialysis)	Yes	Yes
NYHAFC before/after	IV/I	III/I	II/I
Biomarker before/after	CKMB, cTnI/Nil	cTnI/Nil	cTnI/Nil
CRP before/after	22.3 mg/l/ND	15.7 mg/l/ND	41.2 mg/l/ND
Other Tx before/after	CS, CYC, PE/AZA, CS	AZA, CS/AZA, CS	AZA, CS/AZA, CS
Indication for RTX Tx	Refractory	Relapse	Relapse
RTX dosage/schedule#	375 mg/m^2 w × 4	375 mg/m^2 w × 4	375 mg/m^2 w × 4
ECG before/after			
LVEF**	Severe impaired/normal	Severe impaired/normal	Mildly impaired/normal
Chamber enlargement	LAC, LV enlargement/Nil	LV enlargement/Nil	LV enlargement/Nil
LV wall motion	Global hypokinesia/Nil	Global hypokinesia/Nil	Global hypokinesia/Nil
Pericardial effusion	Nil/Nil	Nil/Nil	Yes/Nil
cMRI before/after			
LVEF	Severe impaired/normal	Severe impaired	Not performed
LV wall motion	Global hypokinesia/Nil	Global hypokinesia	Not performed
LV LGE	Global LGE at mid-wall myocardium, epicardium/completely resolved	Global LGE at mid-wall myocardium	Not performed
Endocardium	Endocarditis/partially resolved	Endocarditis with perfusion defects	Not performed
Pericardium	Enhanced pericardium/lessened enhancement	No enhancement	Not performed

* Age at myocarditis onset. # Usage of corticosteroids and cardiac supportive medications for heart failure during the RTX therapy. ** LVEF: mild 46–55%, moderate 30–45%, severe < 30%. MPA: microscopic polyangiitis; RTX: rituximab; MPO: myeloperoxidase; ECG: echocardiograph; ND: not detectable; BVAS: Birmingham Vasculitis Activity Score; FFS: 5-factor score; eGFR: estimated glomerular filtration rate; DA:HHHH: diffuse alveolar hemorrhage; NYHAFC: New York Heart Association Functional Classification; CKMB: creatine kinase-MB; cTnI: cardiac troponin I; CRP: C-reactive protein; PLI: parenchymal lung involvement; Tx: treatment; w: weekly; CS: corticosteroids; CYC: cyclophosphamide; PE: plasma exchange; AZA: azathioprine; LVEF: left ventricular ejection fraction; LAC: lupus anticoagulant; cMRI: cardiac magnetic resonance imaging; LGE: late gadolinium enhancement.

enhancement (LGE) in global LV mid-wall myocardium or plus epicardium in cases 1 and 2, and pericarditis with enhanced thick pericardium in case 1 (Figure 1A). LV endocarditis with perfusion defects was identified in cases 1 and 2. Followup cMRI in case 1 revealed completely resolved LGE at LV myocardium and lessened pericardial enhancement (Figure 1B).

Nonspecific complaint in acute myocarditis such as dyspnea or chest pain is an underdiagnosed cause of acute heart failure[7]. Despite common presentation in admitted patients from this study, acute myocarditis has scarcely been reported in MPA[3], raising the possibility of an overlooked diagnosis. The myocarditis-associated heart failure in MPA can have clinical symptoms and physical signs such as dyspnea and pedal edema mimicking the lung and renal involvement, respectively. Further, myocarditis is not included among initial manifestations before the diagnosis of MPA but as a later development during longterm followup, as demonstrated in our cases. Indeed, the acute myocarditis might not be as rare as previously reported in the patients with MPA, and a survey echocardiograph could help to detect such a critical manifestation.

MPO antibody is an activity marker correlated with BVAS and a predictor of relapse in MPA[9]. Pathogenic roles of B cells in MPA are highlighted by the association of B cell activation with disease activity and the therapeutic efficacy of depleting B cells[10]. Activated B cells can serve as precursors of ANCA-producing plasma cells, and can present autoantigens and provide co-stimulatory signals to autoreactive T cells. B cell depletion with reduced ANCA titers by the RTX usage is an effective CYC alternative for the induction of clinical remission[4]. In this study, after the RTX therapy with complete depletion of B cells, all patients had no MPO antibody, resulting in clinical improvement with reduced BVAS and a recovery of myocardial dysfunction.

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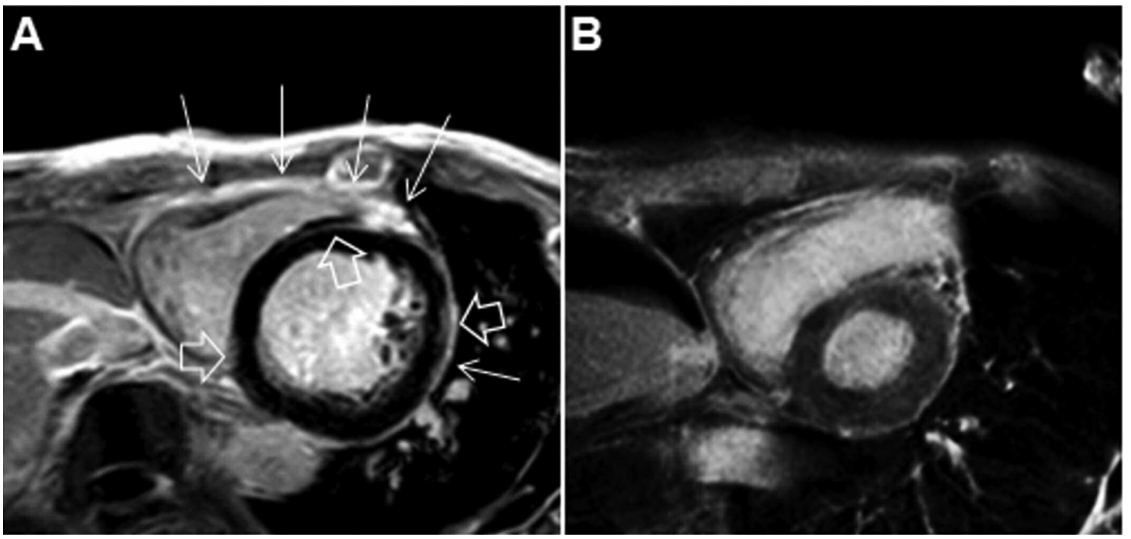

Figure 1. Serial cMRI images of case 1. A. Pre-RTX treatment cMRI late gadolinium enhancement (LGE) image shows pericarditis with enhanced thick pericardium (white arrows) and acute myocardial edema with linear LGE (white hollow arrows). B. Post-RTX treatment image discloses completely resolved myocardial edema and lessened pericardial enhancement. cMRI: cardiac magnetic resonance imaging; RTX: rituximab.