

Catastrophic Antiphospholipid Syndrome

Presenting as Congestive Heart Failure in a Patient
with Thrombotic Microangiopathy

Iulia M. Tulai, MD
Oana M. Penciu, MD
Raymond Raut, MD
Alla Rudinskaya, MD

Thrombotic microangiopathic syndromes are characterized by thrombus formation leading to microangiopathic hemolytic anemia, thrombocytopenia, and end-organ injury that most often affects the kidney and brain. Patients with thrombotic microangiopathy can also present with cardiac involvement, which has been shown to worsen their prognosis. We describe the case of a 46-year-old woman who presented with acute congestive heart failure as a manifestation of catastrophic antiphospholipid syndrome, which is characterized by rapidly progressing multiorgan involvement. Targeted therapy improved our patient's cardiomyopathy and saved her life. Increased recognition of thrombotic microangiopathy as an underlying pathophysiologic mechanism in heart failure and initiation of timely treatment may help to prevent death in patients with thrombotic microangiopathy. (Tex Heart Inst J 2019;46(1):48-52)

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From: Departments of Internal Medicine (Dr. Tulai), Cardiovascular Disease (Dr. Penciu), Nephrology and Hypertension (Dr. Raut), and Rheumatology (Dr. Rudinskaya), Danbury Hospital—Western Connecticut Medical Group, Danbury, Connecticut 06810

Address for reprints:
Iulia M. Tulai, MD,
Department of Internal
Medicine, Danbury Hospital,
24 Hospital Ave.,
Danbury, CT 06810

E-mail: iulia.m.tulai@gmail.com

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Thrombotic microangiopathic (TMA) syndromes share certain defining clinical and pathologic features, such as microangiopathic hemolytic anemia, thrombocytopenia, and end-organ injury.¹ Thrombotic microangiopathy usually manifests itself as renal or cerebral dysfunction, or both. However, cardiac involvement can also occur in the context of these syndromes, and it has been shown to have a significant impact on the mortality rates of patients with TMA.^{2,3} In a study of 220 patients with TMA, 9.5% of the participants developed heart failure, which resulted in a 2-fold increase in mortality rates compared with those in the general population.² We describe the case of a patient with a history of systemic lupus erythematosus, lupus-associated aortic and mitral regurgitation, classic antiphospholipid syndrome, and recent cytomegalovirus (CMV) viremia who presented with acute congestive heart failure as a manifestation of catastrophic antiphospholipid syndrome (CAPS). This case highlights the importance of recognizing TMA as a pathophysiologic mechanism in patients with otherwise unexplained heart failure, as well as administering individualized treatment.

Case Report

In September 2013, a 46-year-old woman was admitted to our hospital with a 2-week history of dyspnea on exertion, orthopnea, lower-extremity edema, and weight gain. A former smoker, she had a history of systemic lupus erythematosus, lupus-associated severe aortic regurgitation and moderate mitral regurgitation, and classic antiphospholipid syndrome, which had been diagnosed in the context of an ischemic stroke and positive and persistent antiphospholipid antibodies. Her father had had coronary artery disease.

Seven months before the current admission, the patient's echocardiograms showed a nondilated left ventricle and normal systolic function. She did not meet criteria for elective valve replacement. She had been on a mycophenolic acid-based immunomodulatory regimen, discontinued in May 2013 after an episode of colitis and CMV viremia.

Two weeks before we saw the patient, she had been evaluated at another clinic for similar symptoms, which were attributed to new-onset nephrotic syndrome. The re-

sults of her kidney biopsy were nondiagnostic. Diuretic therapy was initiated, leading to a transient improvement in her symptoms.

Upon admission to our hospital, the patient was in mild respiratory distress with orthopnea and tachypnea. Physical examination revealed jugular venous distention, heart murmurs suggesting aortic and mitral regurgitation, bilateral lower-extremity pitting edema, bilaterally diminished basal breath sounds, and diffuse livedo reticularis. In comparison with laboratory results obtained one month previously, the patient's brain natriuretic peptide level had increased dramatically to 9,166 pg/mL, and her CMV viral load had decreased from 391,559 to 3,327 copies/mL (Table I). Other notable findings were an increased creatinine level (3.6 mg/dL), decreased hemoglobin level (8.3 g/dL), and new-onset thrombocytopenia (platelet count, $85 \times 10^3/\mu\text{L}$). Her electrocardiogram revealed sinus rhythm with left bundle branch block and a wide QRS complex (150 ms), suggesting severe cardiomyopathy, and her chest radiograph revealed pulmonary vascular congestion. A venous duplex ultrasonogram of the lower extremities showed bilateral soleal vein thrombosis, but a ventilation-perfusion scan indicated a very low probability of pulmonary embolism. Finally, the patient's echocardiograms showed new-onset biventricular systolic dysfunction, dilation of all 4 chambers, and severe mitral and aortic regurgitation (Figs. 1 and 2).

The patient was hospitalized for severe biventricular failure (New York Heart Association functional class IV) of unclear origin. Coronary artery disease, viral cardiomyopathy, valvular cardiomyopathy, lupus-related cardiomyopathy, and TMA were considered in the differential diagnosis. Other active medical problems were acute-on-chronic kidney disease, classic antiphospholipid syndrome, and new-onset nephrotic-range proteinuria, which suggested lupus nephritis.

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Valsartan was continued at 40 mg twice/d as therapy for heart failure, and a low-dose β -blocker (carvedilol, 3.125 mg twice/d) and an intravenous loop diuretic (furosemide, 200 mg twice/d) were initiated. Nevertheless, the patient needed emergency and sustained hemodialysis because of inadequate urine output. The results of coronary angiography were normal, and test results for bacterial endocarditis were negative. Valganciclovir therapy was restarted based on clinical suspicion of CMV myocarditis.

Pulse methylprednisolone therapy (1,000 mg/d for 3 d) was administered for the suspected lupus flare. Mycophenolic acid therapy (500 mg twice/d) was resumed, and hydroxychloroquine therapy (200 mg/d) was continued. Unfractionated heparin was administered for antiphospholipid syndrome. Plasmapheresis was initiated for suspected TMA.

Findings of a renal biopsy (Fig. 3) and a cardiac biopsy (Fig. 4) were consistent with TMA. The patient received a diagnosis of CAPS. Anticoagulation therapy was bridged to warfarin. After 5 sessions of plasmapheresis, the patient's anemia and thrombocytopenia improved, but she still needed hemodialysis for volume control. Intravenous immune globulin and rituximab were also administered according to the lymphoma protocol. The patient's renal function returned to baseline, and her cardiomyopathy resolved. Two months later, she successfully underwent elective double-valve replacement.

At last follow-up 2 years later, the patient's condition was being medically managed with warfarin, carvedilol, and valsartan, and she was stable. Dialysis and diuretics had been discontinued. The patient's lupus symptoms

TABLE I. Results of Laboratory Tests over Time

Variable	Reference Range	Baseline*	Current Admission	Before Surgery**
White blood cells ($\times 10^3/\mu\text{L}$)	4–10	5.7	8.7	5.4
Platelet count ($\times 10^3/\mu\text{L}$)	150–400	229	85	211
Hemoglobin (g/dL)	13.5–17	10.3	8.3	9.4
Blood urea nitrogen (mg/dL)	6–23	22	96	66
Creatinine (mg/dL)	0.67–1.23	2.2	3.63	2.86
BNP (pg/mL)	<100	140	9,166	NA
Urine protein (g/24 hr)	<0.3	0.9	4.88	0.95
CMV viral load (copies/mL)	Undetectable	391,559	3,327	NA
Complement C3 (mg/dL)	70–180	121	82	108
Complement C4 (mg/dL)	10–40	32	16	31

BNP = brain natriuretic peptide; CMV = cytomegalovirus; NA = not applicable

*One month before current admission.

**Two months after the current admission.

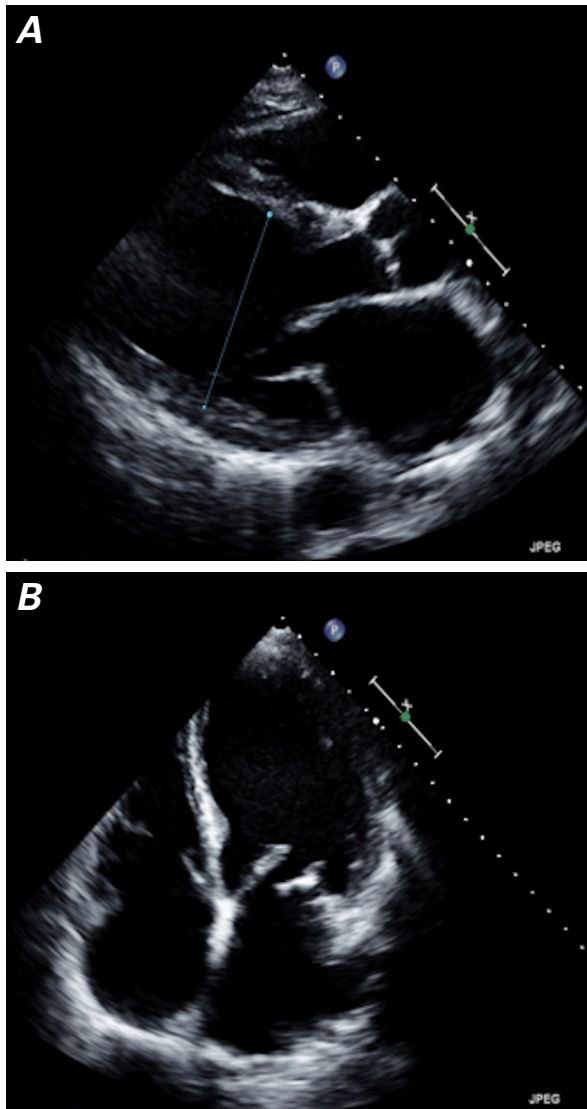


Fig. 1 Transthoracic echocardiograms at admission show dilation of all 4 chambers with **A**) a left ventricular end-diastolic diameter of 7 cm (parasternal long-axis view), and **B**) thickened mitral cusps, which suggest lupus valvulitis (apical 4-chamber view).

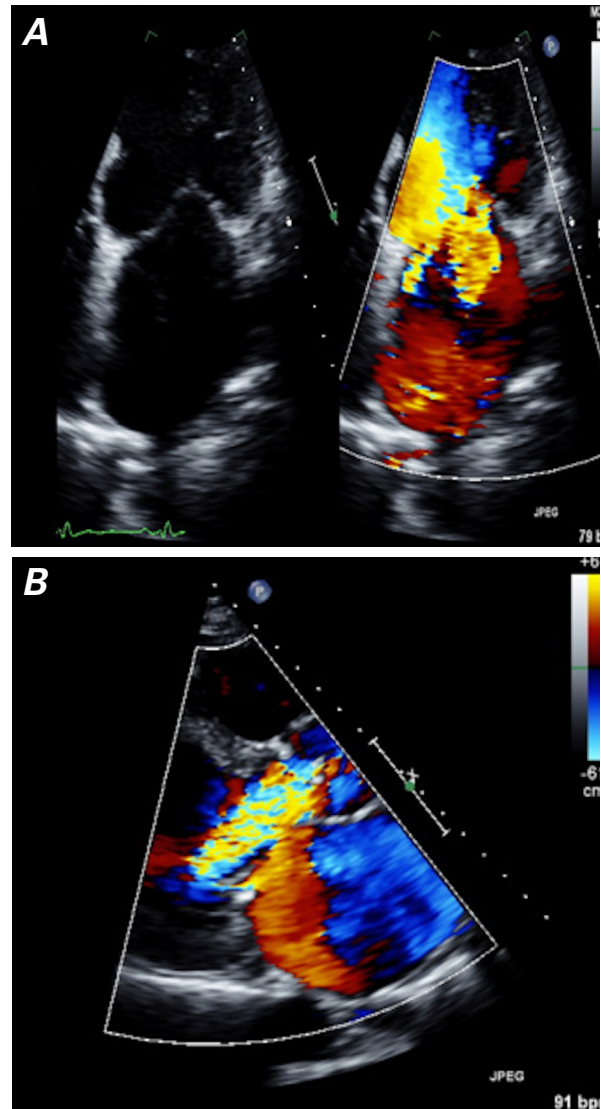


Fig. 2 Transthoracic echocardiograms in color-flow Doppler mode show **A**) an eccentric mitral regurgitation jet and pulmonary venous flow reversal, consistent with severe mitral regurgitation (4-chamber view), and **B**) a wide central aortic regurgitation jet, consistent with severe aortic regurgitation (parasternal long-axis view).

were being effectively controlled with use of mycophenolic acid, hydroxychloroquine, and belimumab. She had no heart failure exacerbations since the one in 2013, and no lupus flares. She continued to visit a rheumatologist every 6 months.

Discussion

Heart failure is a complex clinical syndrome that stems from structural or functional impairment of ventricular filling or ejection of blood, and it may result from disorders of the pericardium, myocardium, or endocardium, or from certain metabolic disturbances. Treatment is somewhat uniform in all patients who have acute heart

failure with reduced ejection fraction; however, regardless of cause, a precise understanding of the mechanism leading to heart failure is crucial for accurate short- and long-term management. Because of our patient's history, identifying the specific cause of heart failure was challenging. Coronary artery disease, viral cardiomyopathy, valvular cardiomyopathy, lupus-related cardiomyopathy, and TMA were considered in the differential diagnosis.

The presence of classic cardiovascular risk factors (smoking history, chronic kidney disease, and family history) and the accelerated atherosclerotic process that has been associated with lupus erythematosus⁴ raised suspicion of coronary artery disease as the cause of heart

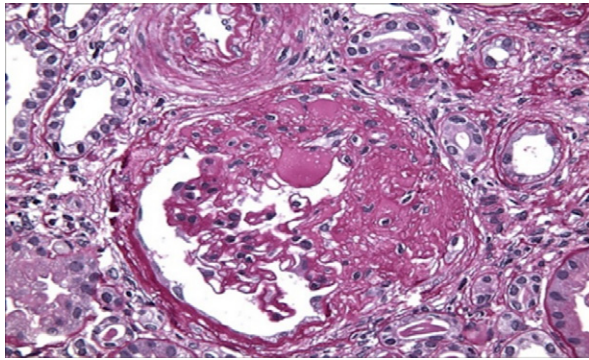


Fig. 3 Photomicrograph of kidney biopsy specimen shows segmental glomerulosclerosis, fibrinoid necrosis of arterioles, and focal thrombosis of the injured vessels, all consistent with thrombotic microangiopathy (periodic acid-Schiff stain, orig. x20).

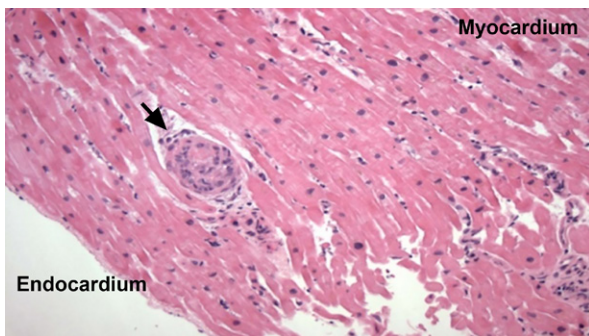


Fig. 4 Photomicrograph of right ventricular endomyocardial biopsy specimen shows multiple thrombi (arrow) in small myocardial vessels and microscopic changes consistent with thrombotic microangiopathy (H & E, orig. x10).

failure in our patient. However, the results of coronary angiography were normal.

Heart failure secondary to viral cardiomyopathy was an important concern in our patient, who was being treated with steroids for recurrent CMV viremia. Most instances of CMV myocarditis occur in immunosuppressed patients, and DNA of CMV can be found in up to 48% of patients with dilated cardiomyopathy and a history of CMV infection.⁵ However, no other clinical signs of CMV infection, such as vision changes, mouth ulcers, diarrhea, fever, lymphadenopathy, or toxic appearance were present. No lymphocytosis was found. The patient's previous viral load of almost 400,000 copies/mL had dramatically decreased to 3,327 copies/mL (Table I). Although CMV myocarditis is unusual at such low viral loads, it was still a possible diagnosis.

Cardiomyopathy related to existing aortic and mitral regurgitation was also considered. However, an inciting event was strongly suspected because of the acute presentation and the concomitant abnormal laboratory findings, which were unexplained. The patient had no signs of bacterial endocarditis according to the modi-

fied Duke criteria, and the results of extensive laboratory evaluation were also negative.

Lupus myocarditis is a rare cardiac manifestation and is mostly asymptomatic,^{6,7} unlike valvular and pericardial disease, which are relatively common in patients with lupus.⁸ Nevertheless, a lupus flare with lupus myocarditis was considered in our differential diagnosis, especially because the patient's mycophenolic acid-based immunomodulatory regimen had recently been discontinued.

Finally, the combination of new-onset thrombocytopenia, worsening anemia, and worsening renal function in a patient with known antiphospholipid syndrome suggested TMA with renal involvement, cardiac involvement, or both.

The results of the minimally invasive workup ruled out some typical causes of acute heart failure but were unable to clearly differentiate between viral myocarditis, lupus myocarditis, and TMA. Individualized therapeutic approaches for these diagnoses are almost antagonistic and, therefore, tissue diagnosis was crucial. Biopsy results proved that microangiopathy was the pathophysiologic mechanism leading to both cardiac and renal failure. The constellation of biopsy-confirmed TMA, known classic antiphospholipid syndrome, and multiorgan dysfunction led to the diagnosis of CAPS.

Catastrophic antiphospholipid syndrome, the most severe form of the syndrome, is characterized by rapidly progressing multiorgan involvement. Specific CAPS therapy reversed the TMA in our patient, improved her cardiomyopathy, and saved her life. There is a need for increased physician awareness of TMA as a predisposing factor for cardiac dysfunction and as a possible pathophysiologic mechanism in patients with otherwise unexplained heart failure, because individualized treatment is paramount to reducing cardiac mortality rates in this population.

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