Cyclophosphamide Restores Heart Function in a Patient with Lupus Myocarditis

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Systemic lupus erythematosus is a multiorgan disease that affects all organ systems including the heart. The cardiac involvement includes almost all the components of the heart. Symptomatic myocarditis is uncommon and is not considered in the standard diagnostic criteria of SLE [1]. Notably, most cardiac dysfunction in patients with SLE is due to coronary artery disease and not myocarditis. We describe a male patient with SLE and myocarditis that was manifested by severe congestive heart failure.

Patient Description

A 45 year old male with recently diagnosed SLE was admitted because of acute pulmonary edema. The patient had no prior cardiac disease or any documented disorders except for epilepsy. SLE was recently diagnosed based on involvement of the skin (photodermatitis), kidneys (proteinuria and red blood cell casts) and blood (hemolytic anemia and leukopenia), as well as positive antinuclear and anti-DNA antibodies. The patient was treated with prednisone and azathioprine. Due to chest pain 2 months prior to admission, the patient underwent coronary angiography and echocardiography, which were normal.

On admission, the patient was in severe respiratory insufficiency and had to be mechanically ventilated. His temperature was 39°C, blood pressure 110/80 mmHg and heart rate regular, 110/minute. Jugular venous pressure was 12 cmH_2O. Breath sounds were decreased with bilateral diffuse crackles over the lung fields. Cardiac examination revealed a regular rhythm, normal S_1 and S_2 and gallop of the third and fourth sounds, with no murmurs or friction rub. Chest X-ray demonstrated enlarged cardiac silhouette and alveolar infiltrates consistent with pulmonary edema. The electrocardiogram recordings showed sinus tachycardia of 110/min and inverted T waves on the anterolateral wall. Echocardiography demonstrated severe left ventricular systolic and diastolic dysfunction with diffuse wall motion hypokinesis. Left ventricular ejection fraction was estimated at 27%. Right ventricular systolic function was normal.

Laboratory findings revealed erythrocyte sedimentation rate of 90 mm/hour, hemoglobin 8.6 g/dl, mean corpuscular volume 92.1 fl, white blood cells 2,700/µl and platelets 262,000/µl, creatinine 2.1 mg/dl, and blood urea nitrogen 39 mg/dl. Red blood cell and white blood cell casts were seen in the urine sediment. A 24 hour urinary collection revealed proteinuria 765 mg. C3 and C4 complement levels were markedly low, while antinuclear and anti-DNA antibodies were higher than 2 months previously. Smooth-muscle antibodies were positive, while rheumatoid factor, ribonucleoprotein, SS-A, SS-B and anti-neutrophil cytoplasmic antibodies were all negative. Electrolytes and hepatic function were within normal limits. Viral serology for enteroviruses, herpes, influenza and Epstein-Barr virus did not indicate an acute infection.

Upon admission the patient was mechanically ventilated: diuretics and morphine were started with clearance of the pulmonary edema. The patient was weaned, and ramipril, carvedilol and spironolactone were added to furosemide.

To further investigate the etiology of the acute heart failure, left heart catheterization revealed normal coronary arteries with markedly reduced left ventricular function. A right heart catheterization was performed [Table]. The procedure was complicated by rapid atrial fibrillation that was converted electrically. An attempt to perform an endomyocardial biopsy was unsuccessful.

Table. Right heart catheterization pressure and saturation measurements before treatment with cyclophosphamide

	Pressure (mmHg) (systolic/diastolic)	Mean pressure (mmHg)	O_2 saturation (%)
Pulmonary artery	51/20	35	66
Right ventricular body	45/10		67
Femoral artery	110/75		98
Right atrium (a/v waves)	16/13	10	68
Pulmonary capillary wedge pressure (a/v waves)	32/40	27	
Cardiac output	5.4 (L/min)		
Pulmonary vascular resistance	1.48 (wood units)		
Systemic vascular resistance	14 (wood units)		

SLE = systemic lupus erythematosus

Presuming that the symptomatic left ventricular systolic dysfunction was due to lupus myocarditis, treatment with pulses of 500 mg intravenous cyclophosphamide was started for 3 days to be followed once a month for 6 months. In addition, the patient was treated with prednisone and hydroxychloroquine sulphate with excellent response. The symptoms of heart failure resolved and the left ventricular systolic function improved gradually, with normal ejection fraction in the last echocardiographic examination that was performed following the last cytotoxic course.

Comment

Myocarditis is an uncommon manifestation in systemic lupus erythematosus; however, it merits an urgent intervention because of the potentially devastating consequences that might lead to death. The clinical manifestations of myocarditis are variable, ranging from subclinical presentation to fulminant pulmonary edema and cardiogenic shock. Patients may present with flu-like symptoms and tachycardia disproportional to the fever. Echocardiography does not establish the diagnosis of myocardits. However, it is important to evaluate the systolic and diastolic ventricular function and chamber size. Endomyocardial biopsy is useful in establishing the diagnosis of lupus myocarditis. Although it is neither specific nor sensitive, it is recommended prior to initiation of anti-inflammatory therapy in these patients [1].

Lupus myocarditis appears to be an immune complex-mediated vascular phenomenon that leads to myocardial injury [1]. Therefore, immunosuppressive treatment modalities may be useful in patients with lupus myocarditis [2–4]. In addition to the standard therapy for heart failure, Sherer et al. [3] reported that high doses of intravenous immunoglobulin improved the cardiac function in a few days with normalization of the ejection fraction (50%) one month later. Chan and colleagues [4] recently described a patient with lupus myocarditis and heart failure that were treated with cyclophosphamide, resulting in significant amelioration of her heart failure symptoms and ejection fraction. Naarendrop et al. [5] also reported a dramatic response to cytotoxic treatment in six patients with SLE who had severe biventricular failure. Their average left ventricular ejection fraction improved from 19% to 40% within 6 months of initiating the treatment [5].

Severe heart failure was the clinical feature of lupus myocarditis in our patient. Treatment with pulses of 500 mg intravenous cyclophosphamide showed dramatic improvement of functional capacity and ejection fraction. It is therefore feasible to consider cytotoxic therapy for patients with lupus myocarditis.

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Erratum

In the article "Neurologic Aspects of Neonatal Hypoglycemia" by A.L. Alkalay, H.B. Sarnat, L. Flores-Sarnat and C.F. Simmons, that appeared in the March issue (IMAJ 2005;7:188–92), several errors occurred in Table 2. We present the correct table below. In addition, ref. 31 in the heading of Table 4 should be omitted.

Table 2. Comparison between hypoglycemia and hypoxia-ischemia brain insult

Parameter	Hypoxia-ischemia	Hypoglycemia
Cause	Reduced oxygen availability	Reduced glucose availability
Serum lactic acid	Increased	Normal
Cerebral cortex	Infarction in watershed zones	Selective neuronal necrosis
Cerebral cortex: layers	Middle laminae, layers 3, 5, 6	Superficial laminae, layers 2, 3, 4
Hippocampus	CA1, CA3	CA1; dentate gyrus
Cerebellum	Purkinje neurons	Absent
Brainstem	Tegmental watershed zone	Absent
Imaging studies	Non-specific	Occipital lobe (occasionally parietal lobe)
EEG	Non-specific	Non-specific, or occipital lobe epilepsy

CA = *Cornu ammonis* (Latin); CA1-CA4 are parts of the hippocampus