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Fulminant Myopericarditis from Phenytoin-Induced Systemic Lupus Erythematosus

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ABSTRACT

Myocarditis and pericarditis are identified at autopsy in up to 50% of patients with systemic lupus erythematosus. However, clinical symptoms of heart failure are unusual, occurring in only 5%-7% of patients. Drug-induced lupus is rare and typically causes classic lupus symptoms of rash, fever, pleuritis, renal insufficiency, and arthritis. We present an unusual case of drug-induced lupus from chronic phenytoin use in a man who presented with symptoms of fulminant myopericarditis. To our knowledge, this is the first such case reported in English.

INTRODUCTION

Systemic lupus erythematosus (SLE) is a connective tissue disease characterized by the presence of autoantibodies and immune complexes. Cardiac involvement occurs in up to 50% of cases.[1-2] SLE can affect any cardiac structure, including the pericardium (12%-48% of cases),[3] valves (13%-65% of cases),[4-5] coronary arteries (25%-45% of cases),[6] conduction system (incidence unknown), and myocardium (10%-40% of cases).[3,7] Drug-induced lupus (DIL) is a well known, albeit rare complication of certain medications including procainamide, hydralazine, quinidine, diltiazam, and phenytoin, and is characterized by the abrupt onset of typical clinical manifestations including arthritis, rash, renal insufficiency, and pleuritis. We present the first reported case of DIL manifesting as fulminant myopericarditis following chronic phenytoin use.

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CASE REPORT

A 57-year-old man with a history of type 2 diabetes mellitus and an isolated episode of generalized tonic-clonic seizure presented to his local emergency department with complaints of worsening pleuritic chest pain for 3 days with radiation to the left neck and ear accompanied by fatigue and dyspnea on exertion. He had been treated with phenytoin 300 mg twice daily, glyburide 10 mg twice daily, and metformin 1000 mg twice daily for the previous 7 years. Physical examination revealed elevated jugular venous pulse, tachycardia, an irregular heart rhythm, crackles in the lung bases, and 2+ lower extremity edema. Electrocardiography confirmed atrial fibrillation with a ventricular rate of 150-180 beats per minute. Transesophageal echocardiography demonstrated normal left ventricular function, an ejection fraction of 60%, and a small pericardial effusion. The patient was successfully electrically cardioverted to normal sinus rhythm. He continued to have pleuritic chest pain after cardioversion and was diagnosed with pericarditis. Naproxen 500 mg twice daily was initiated and he was referred to a cardiologist a week later for further evaluation.

On consultation, the patient complained of continuing positional chest pain with worsening dyspnea and palpitations. Physical examination was notable for a temperature of 37.8ºC, jugular venous distention, bilateral lung crackles, a tachycardic irregular heart rhythm with an audible 2 component friction rub, a small left knee effusion, and lower extremity edema. Electrocardiography demonstrated atrial fibrillation, chest X-ray revealed a severely enlarged cardiac shadow and bilateral pulmonary edema, and laboratory testing was performed (Table 1). Transthoracic echocardiography demonstrated moderate dilation of all cardiac chambers (Figure 1), a left ventricular ejection fraction of 35% with global hypokinesis, diastolic dysfunction, elevated central venous pressure, and a large pericardial effusion with fibrin stranding. Cardiac magnetic

Table 1. Pertinent Laboratory Findings at Presentation

Test	Patient Value	Normal Range
Hemoglobin (g/dL)	10.2	13.6-17.2
Hematocrit (mL/dL)	31	40-52
Platelet (K/uL)	540	160-370
WBC (K/uL)	7.5	3.8-10.5
Differential	77% N, 13% M, 9% L, 1% E, 1% B	
INR	1.7	0.9-1.1
APTT (seconds)	40.8	25-35
Thrombin time (seconds)	24.5	15-20
Cardiac Markers	Negative	Negative
TSH (uIU/mL)	2.35	0.34-5.6 uIU/mL
BNP (pg/mL)	190	0-99
ESR (mm/Hr)	106	0-5
CRP (mg/dL)	34	0-1
ANA	1:2560	Negative
Anti-DS DNA (IU/mL)	2	0-30
SSA (Ro) (U)	2.1	0.0-24.9
SSB (La) (U)	1.8	0.0-24.9 U
Anti-Histone antibody	3	(<1 negative, 1-1.5 borderline, >1.5 positive)
Anti-Cardiolipin antibody	Positive	Negative
Lupus Anticoagulant	Positive	Negative
Direct Coombs	Negative	Negative
UA	0-2 RBC	0-2
Phenytoin (mcg/mL)	9.4	10.0-20.0

ANA=anti-neutrophilic antibody; Anti-DS DNA=anti double-stranded DNA antibody; APTT=activated partial thromboplastin time; BNP=brain natriuretic peptide; CRP=C-reactive protein; ESR=erythrocyte sedimentation rate; INR=international ratio; TSH=thyroid stimulating hormone; UA=urinalysis; WBC=white blood cell count.

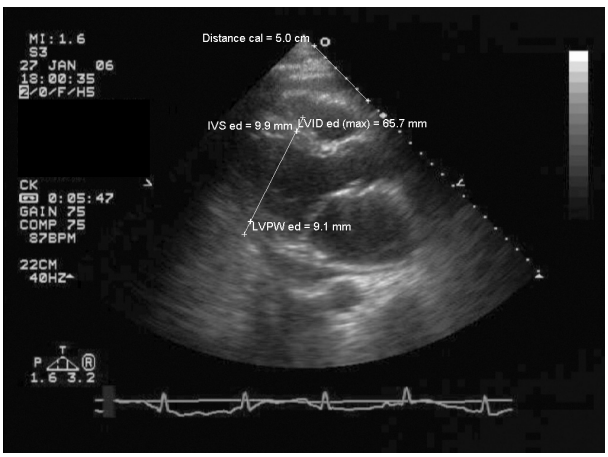

Figure 1. Two-dimensional transthoracic echocardiogram in parasternal long axis view obtained at the time of diagnosis demonstrating an enlarged left ventricle with end diastolic diameter of 65.7 mm (normal <55 mm). IVS=intraventricular septum; LVID=left ventricular internal diameter; LVPW=left ventricular posterior wall; ed=end-diastolic.

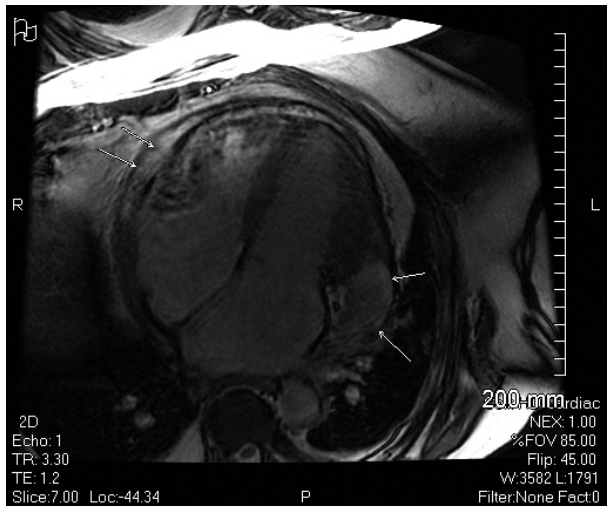

Figure 2. Contrast-enhanced cardiac magnetic resonance image in 4-chamber view demonstrating dilated cardiac chambers and a large, fibrinous pericardial effusion (arrows).

resonance imaging demonstrated global left ventricular hypokinesis with an ejection fraction of 43%, a thickened pericardium with adherence of the visceral and parietal pericardium (Figure 2) but normal left ventricular rest perfusion and no delayed myocardial enhancement to suggest scarring.

The patient was diagnosed with DIL, and phenytoin was discontinued. Methylprednisolone 80 mg daily, colchicine 0.6 mg daily, metoprolol succinate 50 mg daily, furosemide 20 mg twice daily, and lisinopril 5 mg daily were started for left ventricular dysfunction, and warfarin 5 mg daily and amiodarone 400 mg twice daily for treatment of atrial fibrillation. The patient's chest pain and dyspnea improved quickly. The methylprednisolone was transitioned to prednisone 20 mg twice daily and he was discharged home on the remainder of his medical regimen in good condition. An echocardiogram performed a month after discharge demonstrated normal sized cardiac chambers, resolution of the pericardial effusion, and ejection fraction of 65% (Figure 3). The prednisone and colchicine were discontinued, and the patient has had no further episodes of chest pain or dyspnea.

DISCUSSION

Unlike SLE, DIL usually occurs in middle age and both males and females are affected equally. African American patients are seldom affected. Both DIL and SLE are associated with elevated anti-neutrophilic antibody, erythrocyte sedimentation rate, and C-reactive protein. SLE is associated with positive anti-double

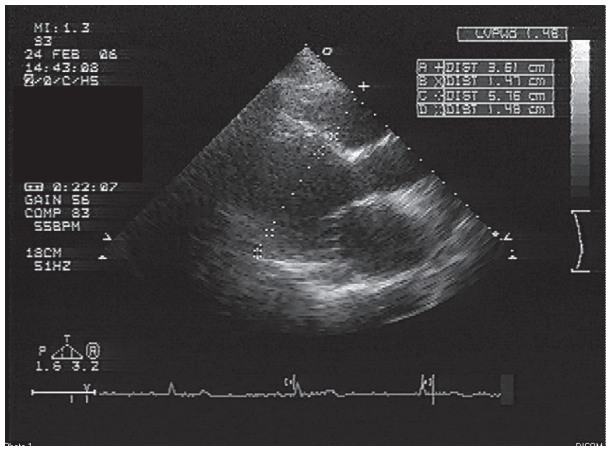

Figure 3. Two-dimensional transthoracic echocardiogram in parasternal long axis view obtained 1 month after discontinuation of phenytoin demonstrating near-normal left ventricular size (end diastolic diameter of 57.6 mm).

stranded DNA antibodies and low serum complement whereas DIL is associated with positive anti-histone antibodies with negative anti-double stranded DNA antibodies and normal complement.

DIL was first reported in association with hydantoin class anti-epileptic agents in 1957.[8] Since then, isolated cases have been reported with symptoms including fever, arthritis, butterfly rash, lymphadenopathy, and renal dysfunction. One German report of mesantoin DIL with symptoms of recurrent seizure, pleuritis, and myopericarditis demonstrated improvement with withdrawal of the drug and treatment with prednisone and chloroquine.[9] We obtained complete symptomatic resolution and return of normal left ventricular size and function by discontinuing the phenytoin, and treatment with moderate dose prednisone and colchicines.[10] This rare case of myopericarditis resulting from DIL stresses the importance of recognizing adverse drug reactions early in a patient's course and treating appropriately.

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