Drug-Induced by Systemic Lupus Erythematosus Presenting as Recurrent Pericardial Effusion After Mitral Valve Repair

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Abstract- We report a patient presented with recurrent pericardial effusion caused by drug-induced systemic lupus Erythematosus (SLE) following mitral valve repair. The surgery was complicated by hemiparesis and convulsion in early postoperative period. The patient had been received carbamazepine for a paroxysmal seizure that occurred following mitral valve repair. The post operative computed tomography showed embolic stroke and its sequel (seizure) that treated with carbamazepine. In the 3rd month of follow-up, however, hemiparesis recovered by physiotherapy but carbamazepine was not discontinued as by request of neurologist. In the 6th month of surgery, the patient admitted by dyspnea and massive pericardial effusion that treated by subxiphoid drainage. This event was re occurred in two times in a short time frame and each event treated by surgical approach. The serologic exam in the last admission revealed drug-induced lupus erythematosus. The carbamazepine as an anti convulsive drug has been described to cause LE like disease in multiple case reports. Laboratory exam exhibited the possibility of carbamazepine-induced lupus in our case, with the extremely rare presentation of recurrent massive pericardial effusion.

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Keywords: Lupus erythematosus; Drug-induced type; Pericardial effusion

Introduction

Carbamazepine is known as an anti convulsing drug but commonly has been used for the treatment of idiopathic pain syndromes, diabetic neuropathy, post traumatic chronic pain syndrome trigeminal neuralgia, and multiple psychiatric diseases (1). Although mild side effects carbamazepine includes, sleepiness, vertigo, ataxia, diplopia, nausea, and vomiting are often easily tolerated by most subjects, but some drug reaction is serious and is potentially lethal and need urgent intervention. These serious side effects include drug-induced SLE, lymphoma-like syndrome, aplastic anemia, blood dyscrasia agranulocytosis (2-4). Here we report a patient who developed recurrent massive pericardial effusion as a severe complication caused by carbamazepine-induced lupus like syndrome (2).

Case Report

A 34-year-old female with a history of a generalized convulsion disorder following mitral valve repair and with a diagnosis of embolic stroke, the anticonvulsant therapy had been started from the time of seizure to 6 months later when she presented to our center with the chief complaint of fatigue, chest pain, and dyspnea. Her symptoms had primarily been attributing to mitral valve problems such as thrombotic complication, prosthetic ring dehiscence, malfunction, or residual regurgitation but a sudden worsening of his dyspnea two hours after admission prompted us to seek an urgent transthoracic echocardiography (TTE) for possible pericardial effusion. His primary vital signs were blood pressure: 70/40 mm Hg; heart rate: 120 beats/per/min; respiratory rate: 32 breaths/per/min; and body temperature: 36.8° C, the patient also had a typical pulsus paradoxus of 18 mm Hg. On physical examination, there was no a crackle or ronchi on chest auscultation bilaterally, and cardiac exam showed vague heart sounds, with the presence of S3 gallop. Laboratory exam showed a therapeutic serum level of carbamazepine of 6 μg/mL (reference range: 5 to 11 μg/mL); blood urea nitrogen: 30 mg/dL; serum creatinine: 1.1 mg/dL; total bilirubin, 1 mg/dL; aspartate aminotransaminase: 34 IU/L; alanine

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aminotransaminase: 25 IU/L ; creatinine phosphokinase, 40 IU/L; leukocyte count, $11.5\times10^3/\mu L$ with a predominant neutrophile count; hemoglobin 13 g/dL; and hematocrit, 40%. A chest radiograph showed a "huge cardiac silhouette (Figure 1), with the absence of pleural effusion or evidence of pulmonary edema. The electrocardiography exhibits normal sinus tachycardia, and low voltages lead to the absence of electrical alternans. An urgent TTE showed a severe global pericardial effusion, with the absence of the right atrium inversion, or diastolic collapse of right ventricular all contributed to severe effusion physiology. An urgent surgical pericardiotomy was undergone with approximately 700 mL of fluid removed. The patient immediately starts to feel the relief of dyspnea and improving her chest discomfort. A routine post discharge echocardiogram showed complete elimination of the pericardial effusion. The routine pericardial fluid analysis revealed a pH of 7.4; RBC count, 8000 cells/μL; WBC count, 2500, cells/μL (neutrophils 70%, lymphocytes 27%, monocytes 3%); protein, 4.5 mg/dL; glucose, 67 mg/dL; and lactate dehydrogenase, 240 IU/L. Laboratory exam for bacterial, tuberculosis, viral, fungal, were negative and pericardium and its fluid cytologic analysis showed no evidence of any malignancy. The postoperative course was unremarkable as echocardiogram did not detect mitral valve stenosis, but mild residual (MR) was observed as other abnormalities such as the left atrial clot formation or reduce cardiac function were not found, the patient was discharged to home with no steroidal anti inflammatory drugs and aspirin daily. 25 days after the discharge, the patient readmitted with an impending filing of choking and dyspnea and was urgently undergoing a TTE and urgently brought to the operating room. The echocardiogram showed a massive pericardial effusion with the diastolic collapse of right ventricle and atrium and impending tamponade. Emergency subxiphoid drainage was accomplished and removed fluid was sent to the biochemical and serological exam. The examination of pericardial fluid devoted the hemorrhagic etiology and results were similar to previous pericardial effusion. The pericardial cytology was negative for malignant causes. The chest tube was left in the pericardial cavity for five days until the absence of effusion was confirmed by TTE control. In addition to no steroidal anti-inflammatory and aspirin, corticosteroids were prescribed, and case discharged to home. After three weeks of discharge, the patient readmitted with a TTE control that showed a new onset of massive pericardial effusion accompanied by a right atrial collapse that was again managed by surgical subxiphoid drainage. As for recommendation of rheumatologist, the patient was scheduled to receive colchicine for 1 month followed by TEE control. The patient readmitted for the third times in 26^{th} days of discharge with signs and symptoms of huge pericardial effusion that again treated with surgical drainage. Considering the failure of the surgical and medical therapy, in the treatment of recurrent effusion, our suspicions focused on the collagen vascular disease and accordingly complete serological exam was performed. During evaluation of our case and positivity of lupus anti nuclear antibody (ANA) test, we noted some rare cases of drug-induced lupus in literature and our attention was paid to carbamazepine. Further laboratory analysis revealed positivity of antinuclear antibodies (1:600), the negativity of anti-double-stranded-DNA (dsDNA), positivity of antihistone antibodies, and negative Smith autoantibody, all continents to the presence of a drug-induced lupus syndrome. Serologic exam for common viral disease that attributing to pericardial effusion was negative. These viral diseases include of echo and coxsackie virus, and HIV virus. A serum inflammatory component of complement levels of C3, C4, and CH50 was also negative. The patient's anticonvulsant drug was changed to phenobarbital and was discharged. Recurrence of the pericardial effusion was not observed in the TEE in the 6^{th} month of follow-up.

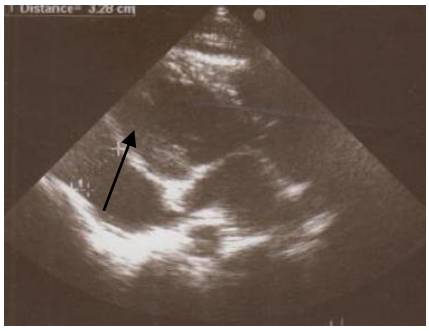

Figure 1. Shows long axis transthoracic echocardiography with local compressive effusion(black arrow)

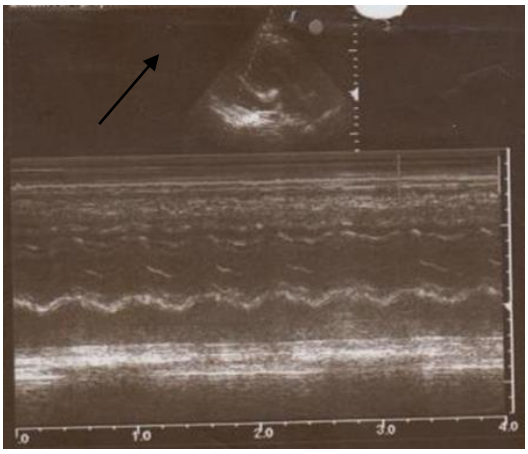

Figure 2. Shows transthoracic echocardiography in four chamber view shows effusion

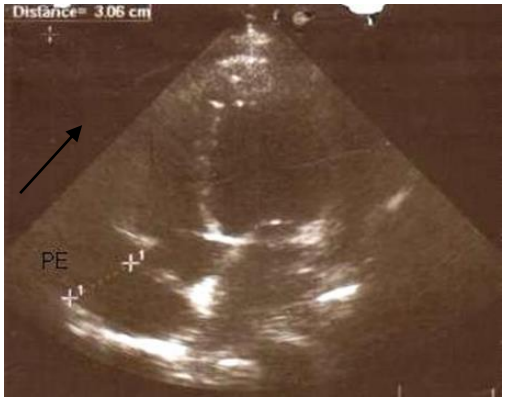

Figure 3. Shows local effusion compressed right atrium

Discussion

Pericardial effusion is a common sequel of cardiac surgery affecting approximately 30% of subjects and occurring within 1-6 months of the primary surgery with a mean of 3 weeks after cardiac surgery (5). The pericardial effusion is truly provoked by an exaggerated response of anticardiac antibody that defined as anti sarcolemmal and anti myocardial fibber antibodies and seems to be a different variant of a provoked post pericardiotomy immune pathologic process (6). Clinical manifestation includes fever, fatigue, malaise, diaphoresis, dyspnea, chest pain, and in laboratory an increased erythrocyte sedimentation rate as well as leukocytosis, eosinophilia, were detected. Some patients may have some degree of normocytic anemia. Hepatic function test is normal, and chest x-ray typically reveals a typical bilateral pleural fluid accumulation by inflammatory pleuritis (7). In contrast to drug-induced effusion, post cardiotomy effusion symptoms usually respond to using of no steroidal anti-inflammatory drugs, aspirin, colchicine or corticosteroids to reduce the fatigue, fever, the chest wall pain, and recurrence of pericardial effusion. Although almost all patients respond to aforementioned drugs and the failure of medical therapy is very rare event, but is possible and may be lead to sequels including, tamponade, constrictive pericarditis, and graft occlusion and needs further extensive laboratory exam to exclude rare causes such as drug-induced lupus and effusion. However multiple criteria have been considered to make the diagnosis of drug-induced lupus, but high index of suspicious is required for virtual detection (8-9). These inclusion criteria include: (1) absence history of known lupus or absence of clinical sign and symptoms of disease or laboratory finding of SLE prior to starting the drug therapy; (2) the occurrence of lupus-like manifestation in course of drug therapy; (3) the early elimination of the lupus-like manifestations within 1-3 weeks of cessation of therapy; (4) serological evidence of antihistone antibodies (5) the completely absence of anti-dsDNA antibodies or presence of very low titers of this antibody (10-11). The presence of antihistone antibodies in 96% of drug-induced cases are highly

suggestive of carbamazepine-induced lupus. However, this antibody exists only in the 50 % of patients with idiopathic lupus. Serologic analyses are usually, the most helpful method in complicated cases. Another useful serologic test in the differential diagnosis of drug-induced lupus is the absence of anti-dsDNA antibodies but is often found in idiopathic lupus SLE in 85% of cases (12). Antinuclear antibodies are not a benefits test in making a distinct differential diagnosis since they are detected in more than 85% of the subjects suffered from either idiopathic or drug-induced lupus (13). In addition to laboratory tests, drug-induced lupus has some clinical symptoms that differentiated these cases from patients with idiopathic SLE. The most frequent clinical finding of drug-induced lupus is skin manifestations that is found in more than 35% of cases but the cutaneous sign is also present in more than 80% of subjects with idiopathic SLE. The kidney and cerebrovascular involvement, however, are exceedingly rare in the drug induced-lupus but being frequent in idiopathic SLE. Pericardial involvement such as pericarditis and effusions accounted for 5% of patients (14-15). The change of the patient's seropositive to negative value regard to antinuclear antibodies, anti-dsDNA, and antihistone antibodies, usually occurred during 1year after discontinuation of drug that without recurrence of pericardial effusion.

However the occurrence of drug-induced lupus is a well-known side effect of carbamazepine therapy, but the development of massive pericardial effusion or tamponade is an exceedingly rare complication of drug-induced lupus. It has been found with some other drugs. In subjects using carbamazepine who develop chest wall pain and dyspnea, it is logical to consider the probability of drug induced cardiac effusion and tamponade or pericarditis, since its prompt diagnosis and drug discontinuation could prevent unnecessarily repeated intervention.

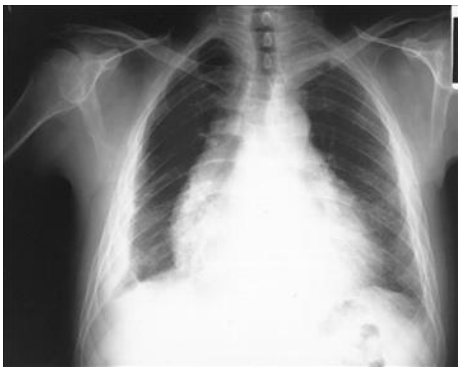

Figure 4. Shows huge cardiac silhoute due to effusion

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