

Dilated cardiomyopathy in the course of thrombophilia

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Abstract: A 40-year-old patient with diagnosed thrombophilia was admitted to the Department due to symptoms suggestive of pulmonary embolism. The imaging results excluded pulmonary embolism; echocardiography revealed dilated cardiomyopathy. The report discusses the association between thrombophilia and possible development of cardiomyopathy.

Key words: thrombophilia, dilated cardiomyopathy

INTRODUCTION

Dilated cardiomyopathy (DCM), the most frequent form of cardiomyopathy, is a myocardial disorder characterized by ventricular dilatation and impaired systolic function, which leads to congestive heart failure and sudden death. There are many etiologies for DCM. The common cause is ischaemic heart disease (ischemic cardiomyopathy): coronary artery disease contributes about two thirds of all cases of heart failure. Other causes of DCM include valvular heart disease, infection, cardiotoxins (e.g., alcohol, chemotherapy), end-stage hypertension [1]. The present paper describes the case of a patient who developed symptoms of dilated cardiomyopathy in the course of thrombophilia.

CASE REPORT

A 40-year-old patient was admitted to the Department of Internal Medicine due to dyspnea at rest, irrespective of body position, non-productive cough and oedema of the lower limbs. These symptoms and an elevated level of D-dimers were suggestive of pulmonary embolism; however, pulmonary CT-angiography did not demonstrate the presence of embolic materials. At the age of 24, he was hospitalized in the Department of Vascular Surgery due to deep vein thrombophlebitis of the left lower limb and thrombosis of the left iliac vein. After 3 years the patient was re-admitted to the Department of Vascular Surgery because of occlusion of the left superficial femoral vein and postphlebitis syndrome at the left lower limb. Phlebography showed thrombosis of the left superficial femoral, external iliac and left common iliac veins. Ulceration developed on the left shin (Figure 1). At the age of 31, the patient was diagnosed with thrombophlebitis of deep veins of the right lower limb. The ultrasound scan demonstrated massive thrombosis within the inferior vena cava reaching the vena cava up to the right iliac vein. The presence of factor V Leiden and reduced anticoagulative protein C activity were found

which evidenced thrombophilia. The level of antithrombin III was normal 88% (normal range from 75% to 125%). At the age of 35, the patient developed symptoms of superficial vein thrombosis of abdominal integuments. One year before the present hospitalization, the patient was diagnosed with class IV cardiac failure according to the NYHA classification. Arterial blood pressure on admission was 140/100 mmHg, heart rate was regular and accelerated to 100/min, whereas BMI was 37.5 kg/m². The Percussion sounds above the lung fields were normal, only at the lung base below the scapula – dull. Vesicular murmur above the lung fields and numerous crepitations at the base of both lungs were found. The liver and spleen were slightly enlarged.



Figure 1 Ulceration of the left shin.

Numerous laboratory and imaging examinations were performed. The blood test results revealed iron deficiency anemia with hemoglobin 10.4 g/dl. The serum level of iron was 44 ug/dl (range 59-158) and concentration of CRP – 25.3 mg/l (normal range below 5 mg/l). The level of NT-pro BNP was high, 4039 pg/ml (normal range below 115 pg/ml). The troponin level was within the reference range whereas the level of D-dimers was elevated – 1537 ng/ml (normal range below 500 ng/ml). The level of creatinine, urea and transaminases were normal.

Electrocardiography revealed tachycardia to 110/min and left ventricular enlargement. Chest X-ray showed the

heart silhouette widened transversely. Doppler ultrasound scanning of lower limb vessels revealed poor flow in deep veins. Echocardiography disclosed dilated cardiomyopathy with severely impaired systolic and diastolic function (Figure 2).

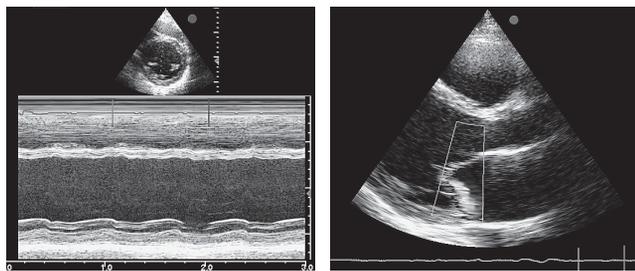


Figure 2 Dilated cardiomyopathy on echocardiography. M-mode scan (left figure) and parasternal long-axis view (right figure) showing dilated left ventricular cavity and reduced movement of interventricular septum and posterior wall of the left ventricle.

The patient was treated with perindopril, spironolacton, carvedilol, furosemid, enoxyparine, acenocoumarol, amiodaron; his symptoms subsided and the general state improved.

The patient was qualified for coronarography and cardioverter-defibrillator implantation.

DISCUSSION

The prevalence of DCM in the population is about 36/10,000, the incidence per year is 5-8/100,000. Familial dilated cardiomyopathy (FDC) may be inherited in an autosomal dominant, an autosomal recessive, or an X-linked manner. Mitochondrial inheritance has also been reported. Most cases of familial dilated cardiomyopathy appears to be autosomal dominant. According to Hershberger *et al.* (2007) this percentage may even reach 80%-90%, whereas X-linked and recessive forms are less common [2]. X-linked diseases associated with DCM include muscular dystrophies (e.g. Becker and Duchenne) and X-linked DCM. DCM may also occur in patients with mitochondrial cytopathies and inherited metabolic disorders such as haemochromatosis. Non-familial causes of DCM include myocarditis of different origin. In most cases the causes are infective, toxic (e.g. cobalt) or immunological (mainly connective tissue diseases). Infectious agents such as viruses (e.g. entero- and adenoviruses), bacteria (e.g. *Borrelia burgdorferi*), Protozoa, Chlamydia or even fungi can begin inflammatory process leading finally to dilated cardiomyopathy. The most common infectious agents identified in patients with DCM seem to be parvovirus B19, human herpesvirus 3, and Epstein-Barr virus [3]. Examples of acquired causes of DCM include also nutritional deficiencies (thiamine, carnitine, selenium), endocrine dysfunction (hypophosphataemia, hypocalcaemia), and the administration of cardiotoxic substances (alcohol, cocaine, amphetamines) or drugs (e.g. doxorubicin and daunorubicin). The thrombophilia states are a special tendency to vein or artery thrombosis that are connected with hematological disorders. In most cases they are habitually presented in young people and often they are recurrent. Thrombophilia can be inherited or acquired. The most often causes of inherited thrombophilia are: the presence of factor V Leiden, prothrombin gene mutation G20210A, protein C or S deficiency, antithrombin III deficiency.

Acquired thrombophilia can be associated with antyfosfolipid syndrome, hyperhomocysteinemia, high plasma level of factor VIII (>150%), IX or XI, plasminogen deficiency, acquired poor anticoagulant response to activated protein C (during pregnancy or as a consequence of oral contraceptives). Factor V Leiden is the most common inherited thrombophilia. It is the result of a specific mutation in the gene for factor V. It is inherited in an autosomal dominant manner. In normal conditions factor V is the co-factor for the activation of factor X, which is necessary for thrombin generation and thrombus formation. Activated protein C is a natural anticoagulant which prevents excessive clot formation in the venous or arterial system. This thrombophilia is characterized by a poor anticoagulant response to activated protein C (APC) and an increased risk for venous thromboembolism. The role of factor V Leiden in arterial thromboembolism is less clear although several cases concerning extensive arterial thrombosis in patients with factor V Leiden mutation were revealed [4, 5]. There are also reports on the association between the factor V Leiden mutation and acute myocardial infarction (AMI) in young patients [6]. Thrombophilia (mutations of factor V, factor VIII, and factor XI; deficiencies of protein C and S, lupus anticoagulant) has been found to play an important role in premature atherothrombosis, especially in young and normolipidemic patients [7].

Patients with antithrombin (AT) III deficiency are susceptible to thromboembolic diseases, particularly deep vein thrombosis of the lower limb and pulmonary embolism. The human AT gene (*SERPINC1*) is located on chromosome 1q23-25 [8], and many defects of this gene have been reported in patients with AT deficiency [9]. Fujimori *et al.* report a case of Japanese patient with combined congenital AT deficiency and DCM [10]. Here, we report a patient with combined congenital thrombophilia and DCM. In our patient the level of antithrombin III was normal, but the presence of factor V Leiden and reduced anticoagulative protein C activity were found which evidenced thrombophilia. Factor V (Leiden) has now been identified as an important cause of hypercoagulability and is present in 18% of caucasian patients with venous thrombosis [11]. Thrombophilia is a risk of venous thromboembolism, and DCM is also a risk of systemic or pulmonary embolization, because blood stasis and low shear rate in the hypocontractile ventricle lead to the activation of coagulation processes [1]. Therefore, the patient with both diseases in combination is likely to be in a highly thrombophilic state.

The antiphospholipid syndrome (APS) is a thrombophilic disorder in which venous or arterial thrombosis, or both, may occur in association with antiphospholipid antibodies. Cardiac manifestations of this syndrome include valvular vegetations and thickening, coronary artery disease, intracardiac thrombi, myocardial dysfunction from cardiomyopathy, or endomyocardial fibrosis. The diffuse cardiomyopathy in APS is most likely a result of multiple myocardial microthrombi [12]. There are several reports of diffuse cardiomyopathy with evidence of microvascular thrombosis without vasculitis. Brown *et al.* reported findings of occlusive thrombosis of intramyocardial arteries with surrounding myocardial necrosis with no evidence of vasculitis in a 22-year-old woman with systemic lupus erythematosus (SLE) and antiphospholipid antibodies who died of heart failure [13].

In an older population, the risk of MI for carriers of factor V Leiden mutation was increased by 40% while the presence of the prothrombin G20210A mutation increased the risk of

MI by 50% [14]. In a subgroup of patients with myocardial infarction, and near normal coronary arteries, Van de Water et al. found increased prevalence of factor V Leiden and prothrombin G20210A mutations [15]. These data suggest that inherited thrombophilia may have a synergistic effect with the other cardiovascular risk factors and may be responsible for development of dilated cardiomyopathy.

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