



Free-floating left atrial thrombi with acquired protein C deficiency in hepatitis

Feridoun Sabzi¹, Reza Faraji^{2*}, Hedayat Heydarizadeh³

Abstract

A 43-year-old woman with a recent history of confirmed hepatitis B presented with yellow sclera and dyspnea. Clinically, she had tachycardia and tachypnea as well as signs of jaundice and right upper quadrant pain. She was in sinus rhythm with a normal aspect of cardiac examination. She was treated with corticosteroids and her symptoms were partially relieved, however, her mild fever remained unchanged and a transthoracic echocardiogram (TTE) and transesophageal echocardiography (TEE) were done to rule out embolic or in situ infective endocarditis. Images from the TEE and TTE showed a ping-pong-like clot in the left atrium with a normal cardiac function and a normal mitral valve function. The mitral leaflets appeared to be normal with no regurgitation, and no clot was noted in other chambers or valves, including the atrial appendages. A differential diagnosis of infective vegetations, clots, or tumors was considered. The three subsequent blood cultures were negative. A complete thrombophilia assay revealed a severe reduced protein C factor, however, the IgG anti cardiolipin and lupus anticoagulant were normal. The woman's anti-nuclear antibody and anti-double-stranded DNA were negative, confirming the diagnosis of acquired protein C deficiency. The patient underwent an open surgical removal of the clot and postoperative treatment with steroids, warfarin, and heparin. The postoperative course was uneventful, and the patient was discharged on the 13th day of operation in good condition. This case was interesting because we did not find any mitral valve pathology such as mitral stenosis, or arrhythmia like atrial fibrillation.

Keywords

left atrial thrombi, protein C deficiency, hepatitis

Introduction

In blood plasma, protein C is a vitamin-K-dependent serine protease synthesized by the liver. The activated protein C, which is the active form of protein C, with the inhibition of coagulation factors and the stimulation of fibrinolysis, makes coagulation's system within normal balances. Protein C is produced in the liver as a single sequential protein and after several post-translational changes in the mitochondria, including the carboxylation of glutamic acid remainder, the hydroxylation of acid aspartic leftover, and the glycosylation process, it is converted into an active form [1]. Plasma protein C levels are related to the hepatic function, and in hepatic failure, the plasma level rapidly reaches the minimum level. Protein C levels fall more rapidly than other vitamin-K-dependent proteins when synthesis is altered by the administration of oral anticoagulants or in transient liver dysfunction, as in viral hepatitis. Generally, low serum levels of protein C are a highly sensitive indicator of hepatic function. In the post-liver-transplantation period, regarding any cause of irreversible hepatic failure, plasma protein C levels may be a sensitive marker for the probability of success or rejection of the transplantation [2]. Except for hepatic dysfunction, acquired protein C deficiency occurs in a variety of diseases such as septic shock, acute inflammatory process, disseminated intravascular coagulation, acute venous or

arterial thrombosis, and in the administration of a variety of drugs such as L-asparaginase, warfarin, or drugs used in chemotherapy. In overwhelming sepsis, deficiencies of activated protein C may be severe due to the presence of a combination of multiple factors that decrease protein C levels and down-regulate the output of the thrombomodulin factor and endothelial source of the protein C receptor [3]. Some cases of protein C deficiency have also been reported with an anti-APC antibody, bone marrow transplantation, prolonged hemodialysis, inflammatory bowel syndrome, post-Fontan operation for a single ventricular anomaly, acute myelogenous leukemia, and hepatocellular carcinoma [4]. Left atrial ball thrombi have not been reported in patients who have had mild mitral stenosis without concomitant atrial fibrillation. Kuo et al. report the first case of left atrial ball thrombus in a patient with a normal mitral valve with atrial fibrillation, since then, Yu et al. and Kaneda et al., in two separate studies, covered two cases of left atrial free floating ball thrombi in the absence of mitral valve disease with atrial fibrillation (AF) reported [5-7]. Almost all patients with a left atrial free floating ball thrombus with or without mitral stenosis have atrial fibrillation. Besides AF, predisposing factors in the left atrial free clot are mitral stenosis, a post mitral valve replacement state, myocardial infarction, any type of myocarditis, dilated or hypertrophic cardiomyopathy, and infective endocarditis [8]. The etiological mechanism of left atrial free floating ball thrombus in our patient with no evidence of these cardiac diseases, or others with a thrombophilia state and atrial fibrillation, is related to hepatitis-induced protein C deficiency. We speculated that a fixed thrombus in a non-rheumatic left atrium without mitral stenosis or in others with a valvular pathology is formed as a result of an acute deficiency of protein C with concomitant bed rest and immobilization of hospital stays. The endocardium, particularly on the mitral valve leaflet, is vulnerable to

*Corresponding author: Reza Faraji, Tuberculosis and Lung Diseases Research Center, Ilam University of Medical Sciences, Ilam, Iran; E-mail address: r.faraji61@gmail.com; Tel: +98 9183362603; Fax: +98 831 9360043

¹Department of General Surgery, School of Medicine, Kermanshah University of Medical Sciences, Kermanshah, Iran

²Tuberculosis and Lung Diseases Research Center, Ilam University of Medical Sciences, Ilam, Iran

³Department of Pediatric, Faculty Member School of Medicine, Ilam University of Medical Sciences, Ilam, Iran

injuries due to shear stress, jet effect, and turbulence. Micro injuries expose phospholipids on superficial valve structures or on endothelial cells of intra valvular capillaries and the binding of autoantibodies to the phospholipids-antigen complexes produced in hepatitis B, causing an endocardial cell activation and microscopic spots of thrombosis [9]. These micro clots, by the natural fibrinolysis mechanism, switch into fibrotic tissue or completely melt on the valve. In a hypercoagulable state, as seen in our patient, this micro clot gradually grows into the left atrial cavity and forms a spherical shape. The final disconnection of the pedicle between the thrombus and the atrial wall caused thrombosis as a free ball-shape clot.

Case report

A 43-year-old woman was admitted to a general hospital complaining of arthralgia and jaundice, with a diagnosis of acute hepatitis B. Neither arrhythmia nor valvular heart disease were present in her medical history. Her present symptoms were complicated with a cerebral symptom as there was hemiparesis eight days following admission. Computed tomography scans of the brain did not reveal any significant lesions. Electrocardiograms revealed a sinus rhythm that was normal. Atrial fibrillation had not been mentioned by her. On transthoracic echocardiography, there was a large, round, pedicled mass floating in the left atrium during systole and it was migrating into the mitral orifice during diastole, but its large size prevented its migration to the left ventricle (Figures 1, 2). After undergoing an urgent cardiac operation, the ball thrombosis was removed from the patient. With aortic cannulation and bicaval venous drainage, a cardiopulmonary bypass was established. Using antegrade warm blood cardioplegia, the aorta was cross-clamped and the heart was arrested. In the left atrium, an attachment-free ball-like mass was discovered following a longitudinal atriotomy of the right atrium by a trans-septal approach (Figure 3). There was no evidence of any other thrombus in the left atrium. The mass looked like a round ball and was removed. Cardiopulmonary bypass was discontinued after the right atrium was closed. Postoperatively, the patient was prescribed warfarin for anticoagulation. The patient was then discharged from the hospital on postoperative day five in a stable condition to her previous internal ward. A four-month follow-up period revealed no further embolic events. In terms of shape, the removed clot was oval, a homogeneous dark color, and had an elastic consistency. The mass measured 30 304 mm in diameter and weighed 17 grams. Upon histological examination, it was determined that the thrombus was organized (Figure 4).

Discussion

In this patient, the underlying protein C deficiency was secondary to hepatitis and compounded by immobilization and confinement to bed during the initial phase of illness, which appears to have provoked the onset of the thrombosis. Rečičárová et al. reported a case of a free-floating clot in left atrium in a patient with mitral stenosis that operated with mitral valve replacement and clot removal. No new

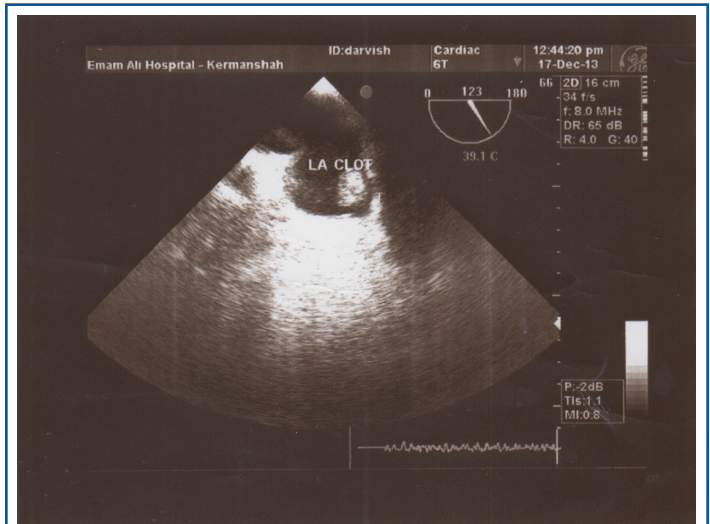


Figure 1 - Clot free in the left atrium.



Figure 2 - Left atrial circumferential clot.

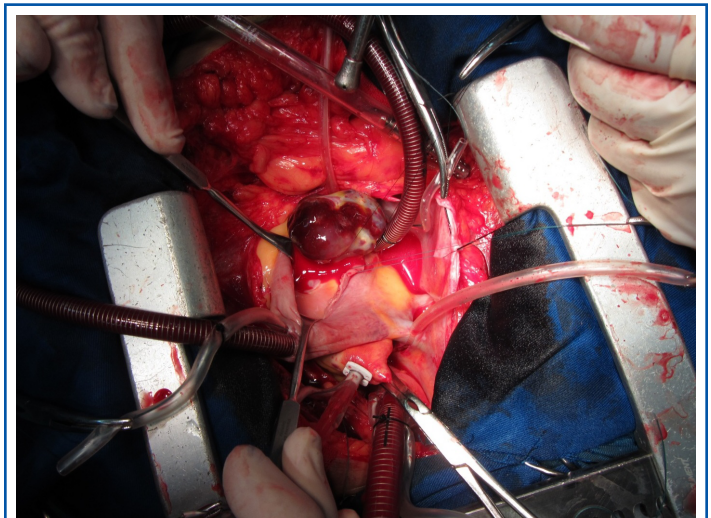


Figure 3 - Excision of a transseptal left atrial clot.

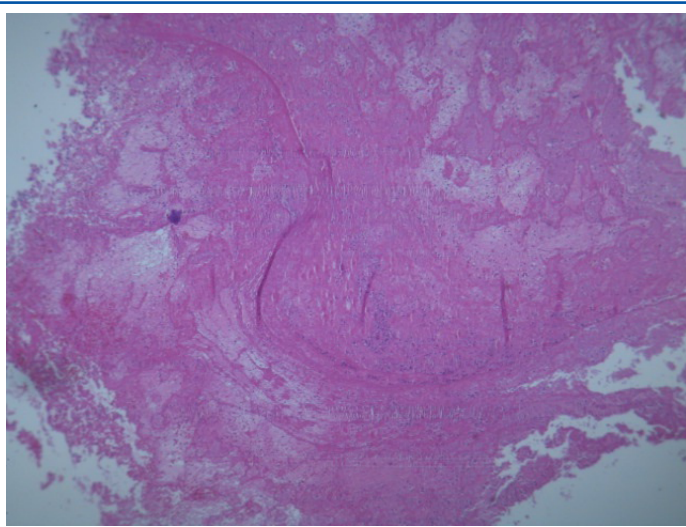


Figure 4 - A microscopy image of the clot.

finding was found in their case report [10]. Kaneda et al. reported two cases of ball emboli in the left atrium in two cases with mitral stenosis, and one of their patients had renal failure [7]. Akhmerov et al. reported a case of a ball clot in the left atrium in a patient with biventricular failure and mitral stenosis that was removed by surgery; however, this article did not add new findings to medical literature [11]. Palmer et al. reported a rare case of a left atrial clot after a transcatheter aortic valve replacement, and the background disease in this case was atrial fibrillation [12]. The actual incidence of protein C deficiency in our population is not known. However, no study has been designated to determine the pathogenesis underlying cardiac thrombosis in patients with acquired protein C deficiency. The inherited hypercoagulable states include protein C and S deficiencies, activated protein C resistance, antithrombin III deficiency, dysplasminogenemia, dysfibrinogenemia, and high levels of the plasminogen activator inhibitor [9]. Natarjan et al. reported a case of AIDES in a patient that presented with right atrium thrombosis, and the cause of thrombosis was right heart failure [13]. In Miyata et al.'s study, the acquired hypercoagulable states were antiphospholipid syndrome and thrombocytopenia [9], and Saxena et al. showed that a severe bacterial or viral illness can cause acquired protein C deficiency [14]. Protein C's system constitutes one of the major regulatory systems of hemostasis. Protein C is a vitamin-K-dependent proenzyme synthesized in the liver. On the surface of endothelial cells, thrombin binds to a receptor known as thrombomodulin. This complex is the site for the interaction with protein C. Once bound to this complex, protein C becomes activated (activated protein C). Protein S acts as a cofactor in this process. When activated, protein C inhibits factor VIIIa and factor Va (interfering with the two rate-limiting steps of coagulation cascade), thus, exhibiting its anticoagulant property. Also, activated protein C enhances fibrinolysis through the inhibition of the plasminogen activator inhibitor. Hence, if there is a deficiency of protein C or if there is a resistance to activated protein C (which is secondary to factor V Leiden mutation), there results a prothrombotic state in which the presence of reduced fibrinolysis

leads to clinically manifesting thrombosis [15]. Khalid et al. reported a case of left atrial thrombosis mimicking a myxoma in a patient with lupus erythematosus [16]. A hyper coagulant state without mitral valve stenosis was the leading cause of the clot. Hilgartner et al.'s study acquired causes of protein C deficiency including liver disease, DIC, therapy with L-asparaginase and warfarin, and acute severe bacterial or viral infection [17]. The management of acquired protein-C-deficient patients with cardiac chamber thrombosis is with heparin anticoagulation, which is prescribed either with conventional or low molecular weight types. Gerson et al. revealed that in cases of acute severe protein C deficiency with clinical manifestation of thrombosis, protein C concentrates or fresh frozen plasma therapy is essential [18]. Gerson et al. showed that there was resistance to both heparin and warfarin during the initial few days of the commencement of therapy. In their study, causes like non-compliance, malabsorption, known drug interactions, laboratory errors, and excess vitamin K in the diet were considered and ruled out [18].

Conclusion

In conclusion, under rare circumstances, a protein C deficiency in mild mitral stenosis can result in left atrial thrombosis. Our patient did not have mitral stenosis, however, it is commonly believed that the incidence of thrombosis in mild MS is exceedingly rare in adults, given the absence of an underlying cardiovascular condition. The presence of a left atrial free floating ball thrombus may be expected to indicate higher embolic potential. There is a possibility of sudden death caused by the occlusion of the mitral orifice by the ball thrombus. In patients with a left atrial free floating ball thrombus, prompt surgical removal is recommended to prevent catastrophic complications such as cerebral vascular incidents and sudden circulatory arrest. Surgical removal of a left atrial free floating ball thrombi using a cardiopulmonary bypass is the first therapy of choice, because it can safely prevent critical complications and further systemic embolic events.

Author Contributions

This study was designed and managed by Feridoun Sabzi and Reza Faraji.

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None.

Conflicts of Interest

The authors declare that they have no conflict of interest.

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