

Intracardiac Thrombosis in Sickle Cell Disease

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What's Known

- Sickle cell crisis has been previously considered the only venoocclusive disease leading to organ failure.

What's New

- In the present study, endothelial injury occurred in sickle cell crisis and led to the release of large amounts of von Willebrand factor, which induced vascular thrombosis.

Abstract

In patients with sickle cell disease, thrombotic microangiopathy is a rare complication. Also in sickle cell disease, intracardiac thrombus formation without structural heart diseases or atrial arrhythmias is a rare phenomenon. We herein describe a 22-year-old woman, who was a known case of sickle cell- β thalassemia, had a history of recent missed abortion, and was admitted with a vaso-occlusive crisis. The patient had manifestations of microangiopathic hemolytic anemia, including laboratory evidence of hemolytic anemia, thrombocytopenia, respiratory distress, fever, jaundice, and abnormal liver function and coagulation tests, accompanied by clot formation on the Eustachian valve of the inferior vena cava in the right atrium and also a long and worm-like thrombus in the right ventricle. Therapeutic plasma exchange improved her clinical condition, and her intracardiac thrombus was completely resolved after 1 week. Echocardiography, as a simple and inexpensive imaging modality, had a significant role in the diagnosis and follow-up of this patient.

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• Plasmapheresis

Introduction

Sickle cell disease (SCD) results from the inheritance of a mutant β -globin allele, yielding rigid, adhesive, lysis-prone erythrocytes. A bulk of evidence shows platelet and plasma coagulation activation in SCD.¹ Several adhesive, lysis-prone erythrocyte molecules have been implicated in sickle vaso-occlusion, including von Willebrand factor (vWF), which is a multimetric glycoprotein involved in platelet adhesion.¹ Endothelial cells, when activated acutely, can release very large amounts of huge and hyper-adhesive vWF molecules capable of binding to platelets and erythrocytes spontaneously, especially sickle cells. There is a significant role for hyperactive vWF in SCD pathology.² The vaso-occlusive and hemolytic complications of SCD are well known, and other clinical manifestations of this hypercoagulable disease such as large-vessel thrombosis, and in rare cases, intracardiac thrombus are also noteworthy.^{1,3}

We herein present a rare case of clot formation in the right atrium and ventricle in a young woman with SCD with a presentation of microangiopathic thrombosis.

Case Presentation

A 22-year-old woman, who was a known case of sickle cell- β thalassemia (Hb S/ β Th) with no previous hospitalizations due

to other underlying medical disorders, suffered a missed abortion and underwent dilation and curettage 1 week prior to her admission to our institution. The patient experienced fever, hypogastric pain, and malodor yellowish vaginal discharge. Her fever increased gradually and was followed by chills, dark-colored urine, and back pain. With the primary impression of sickle cell crisis and pelvic inflammatory disease, she was admitted to our institution, Shahid Mohammadi Hospital (a referral general hospital in the southern Iranian city of Bandar Abbas), in June 2013. Oral consent was obtained from the patient. She complained of dyspnea and generalized bone pain on admission. She had no history of consuming alcohol or any drugs and medications. Her physical examination revealed only pallor and mild tenderness of the hypogastric region. She had a white blood cell count of $7100/\mu\text{L}$, hemoglobin level of 6.5 g/dL , platelet count of $80000/\mu\text{L}$, and creatinine level of 0.5 mg/dL . The laboratory findings were in favor of hemolytic anemia (i.e., elevated lactate dehydrogenase, 5687 IU/L and indirect hyperbilirubinemia, total, 3.5 ; direct, 1).

The patient received an isogroup packed cell and normal saline for her dehydration and anemia.

On the second day of admission, her dyspnea exacerbated following the packed cell transfusion. An emergency echocardiographic examination was performed to evaluate cardiac function and possibility of heart failure. Transthoracic echocardiography (TTE) and also transesophageal echocardiography (TEE) showed normal left and right ventricular size and function, mild pulmonary hypertension (systolic pulmonary artery pressure, 37 mm Hg), and dense echogenicity on the Eustachian valve of the inferior vena cava in the right atrium and a worm-like, highly mobile echogenicity ($5\times 0.4\text{ cm}$) in the right ventricle attached to the free wall without valvular involvement, mostly in favor of intracardiac thrombosis (Figures 1 and 2).

The patient's dyspnea exacerbated and was accompanied by a high-grade fever. She was transferred to the intensive care unit for intensive care. Meropenem, ampicillin, gentamycin, and vancomycin were started empirically after consultation with an infectious disease specialist. The spiral chest computed tomography (CT) scan was in favor of the acute respiratory distress syndrome. Spiral chest CT angiography and Doppler sonography did not demonstrate deep vein thrombosis or evidence of pulmonary thromboembolic disease. Thrombotic microangiopathy was suspected given the patient's underlying disease (i.e., Hb S/ β Th),

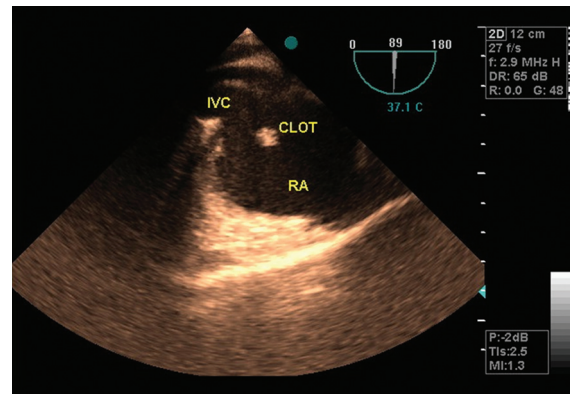


Figure 1: Transesophageal echocardiography shows a clot on the Eustachian valve (valve of the inferior vena cava) in the right atrial cavity.

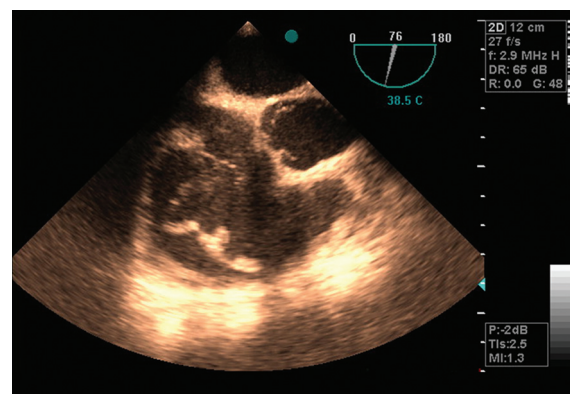


Figure 2: Transesophageal echocardiography shows a worm-shaped clot in the right ventricular cavity.

peripheral schistocytes, and other laboratory data. She underwent plasmapheresis 10 times until her platelet count was in normal range (1 week later). After platelet normalization, ASA and enoxaparin were started and after 5 days, a repeated TEE showed a significant decrease in the size of the echogenic right ventricular mass ($1.38\times 0.4\text{ cm}$) and disappearance of the echogenic mass on the Eustachian valve of the inferior vena cava, confirming intracardiac thrombosis.

The patient's laboratory data showed a white blood cell count of $4800/\mu\text{L}$, hemoglobin level is 13.3 gr/dL , platelet count of $191000/\text{mL}$, serum creatinine level of 0.8 mg/dL , and lactate dehydrogenase level of 994 IU/L . She was discharged in good condition with warfarin and ASA, and her thrombus was completely resolved. Follow-up TTE and TEE 1 month later were completely normal without any thrombosis.

Discussion

Thrombus formation in the right side of the heart without underlying structural heart diseases or atrial fibrillation is rare.⁴ Free-floating right-sided

thrombi seem to be a severe form of venous thromboembolism originating from deep vein thrombosis.⁴ Spontaneous right-sided heart thrombi have been detected in hypercoagulability states such as protein C deficiency, Bencher's disease,^{5,6} inflammatory bowel disease,⁷ and antiphospholipid antibody syndrome and rarely in SCD due to thrombotic microangiopathic processes.⁸

We found only 2 case reports of cardiac thrombosis in SCD in our literature review. One of the cases was a 52-year-old man with pulmonary hypertension due to chronic pulmonary thrombosis and a history of splenectomy 26 years previously: He presented with acute dyspnea and pleuritic chest pain and was admitted with the diagnosis of acute pulmonary thromboembolic disease. Echocardiography showed a large free-floating thrombus in the right atrium, and it extended to the right ventricle and the main pulmonary artery. Streptokinase was initiated and within 21 hours, the thrombus was resolved and the patient was discharged with aspirin and warfarin.³ The second case was a patient with SCD with the acute chest syndrome without response to exchange transfusion. The patient had a right atrial thrombus and antiphospholipid antibody. The thrombosis was resolved through the administration of thrombolytic therapy.⁸

Our patient had no underlying pulmonary hypertension or acute pulmonary thromboembolic disease or other procoagulant diseases. Her sickle cell crisis was triggered by pelvic inflammatory disease following a missed abortion. Clinical and paraclinical findings, including chest pain, fever, respiratory distress, abnormal liver function, coagulopathy, thrombocytopenia, and schistocytosis, are explainable with thrombotic microangiopathy in this patient. Clot formation in the right atrium and the right ventricle in this patient may have been due to the high level of vWF activity.

Secondary thrombotic microangiopathy can be induced by a large number of disorders such as malignancy, infection, disseminated intravascular coagulopathy, autoimmunity, chemotherapy drugs, and rarely sickle cell crisis. Therapeutic plasma exchange (TPE) is the choice of treatment for idiopathic thrombotic purpura and is ineffective in most cases of secondary thrombotic microangiopathy. Nonetheless, Shome et al.¹ reported 10 cases of SCD with documented thrombotic microangiopathy: Nine cases recovered completely with TPE.

Given our patient's uncomplicated intracardiac thrombosis and ongoing coagulopathy, we performed TPE and plasmapheresis. TPE significantly improved the clinical condition of the

patient and decreased the size of her intracardiac thrombus. It is important to note that our patient first underwent repeated plasmapheresis until the resolution of her coagulopathy and thrombocytopenia (1 week later) and then received ASA and enoxaparin. Moreover, she received no anticoagulation and antiplatelet treatment despite the coagulation disorder in the early course of her disease. Therefore, it seems that the main factor in the shrinkage of the clot was the plasmapheresis not the anticoagulant medication.

For all the laboratory evidence in favor of hypercoagulability in patients with SCD, the role of anticoagulants and antiplatelet agents is not clear in clinical studies.^{1,9} Most of these studies are small or poorly controlled, and it is still unclear whether the observed platelet activation and increased thrombin and fibrin formation contribute to the vascular occlusive episodes or whether they are a simple epiphenomenon.

Conclusion

Thrombotic microangiopathy in patients with sickle cell syndromes, especially intracardiac thrombi without underlying structural diseases or atrial arrhythmias, is a rare complication. In such patients with acute deterioration, however, high clinical suspicion can confer an early life-saving diagnosis.

The importance of echocardiography, as a simple, noninvasive, and rapid investigation for detecting intracardiac thrombi, is clear and our report further underscores this fact. Early plasmapheresis seems to be the main reason for the resolution of the thrombosis in our patient.

Conflict of Interest: None declared.

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