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Case report

Prothrombotic role of antiphospholipid antibodies in a patient with sickle cell disease

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Abstract: Sickle cell disease (SCD) is a common inherited condition in African, Caribbean, and Mediterranean countries. SCD is a hematologic disorder caused by a well-characterized point mutation in the β-globin gene, which produces an abnormal hemoglobin S that results in the sickling of red blood cells in deoxygenated conditions. Patients with SCD display a "hypercoagulation state" leading to an increased risk of severe venous and arterial thrombotic vascular events. Herein we report a case of severe thrombotic complications in a patient with SCD who showed high antiphospholipid antibodies (APA) levels during vascular occlusions.

Keywords: antiphospholipid antibodies; sickle cell disease; hypercoagulation state; thrombotic complications

1. Background

Sickle cell disease (SCD) is characterized by chronic intravascular hemolysis, vascular occlusions, painful and multiple organ damage [1]. It also presents chronic activation of the coagulation system responsible for vaso-occlusive crises and venous thromboembolism (VTE) [2,3].

To date, the frequency of coexisting SCD and APA has not been well evaluated, and most data come from but a few case reports [4,5]. The connection between high APA levels and sickle cell syndrome and its impact on major thrombotic complications of SCD has not been adequately investigated [6]. Interestingly, in our case report, serum APA levels were remarkably high, and we hypothesize that APA may play a prothrombotic role in SCD.

2. Case history

The patient is a 47-year-old Caucasian woman affected by severe SCD, genotype S/S (homozygous sickle cell). Her clinical history was characterized by a mild ischemic stroke episode that occurred at the age of 30 years old, after which she started taking cardioaspirin and was administered monthly transfusion therapy with careful monitoring of HbS. At that time HbS was 45% and Hgb was 7.5 gr/dL, she also performed a transcranial Doppler and cerebral magnetic resonance angiography with evidence of sickle vasculopathy, not moyamoya-like. Given the ferritin levels remained at values of 1500–2000 ng/mL, she underwent iron chelation therapy with deferasirox 20 mg/kg (patient's weight: 80 kg) with satisfactory results. In October 2019 she suffered a severe stroke and was admitted to the emergency department by her husband, she was found to have altered mental status, right hemiplegia, and aphasia. On triage, the patient had a body temperature of 36.5 °C, blood pressure of 140/80 mmHg, heart rate of 72 beats per minute, respiratory rate of 20 breaths per minute, oxygen saturation of in-room air, and blood sugar of 350 mg/dL. The patient was not articulating or able to communicate history. Physical examination revealed global aphasia, uncooperativeness, left gaze deviation, spastic hypertonus, severe right facial brachial hemiparesis, right hypoesthesia, right spatial inattention, and signs of Babinski on the right. National Institutes of Health Stroke Scale (NIHSS) 19.

Initial laboratory investigations revealed severe leukocytosis, normochromic normocytic anemia, elevated reticulocyte count, total bilirubin, lactate dehydrogenase, and a baseline of 42% HbS.

An electrocardiogram showed sinus tachycardia. There was no radiographic evidence of acute pulmonary disease on the chest X-ray. A computed tomography (CT) scan without contrast of the head was performed in the emergency department, which did reveal a parenchymal hypodensity area with cortico-subcortical distribution in the left fronto-insular and temporoparietal region with extension to the nuclei of the ipsilateral base; it modestly marked the ipsilateral lateral ventricle.

Therefore, she was admitted to the neurological division unit for a suspected cerebrovascular accident and was given aspirin 125 mg, atorvastatin 80 mg, enoxaparin sodium 6,000 U.I., fondaparinux sodium 2.5 mg/day, mannitol 18% 100 mL × 4/day, and rehydration therapy.

The patient was treated with thrombolysis and thrombectomy of the upper and intermediate Sylvian trunk. On day 2, the patient was not alert, oriented, or able to answer questions appropriately. A magnetic resonance imaging (MRI) without contrast of the brain (T2 FLAIR (T2-weighted fluid-attenuated inversion recovery)) showed restoration of the flow signal in the context of the left Sylvian axis. A carotid duplex ultrasound revealed less than 50% stenosis of the right internal carotid artery and a normal left internal carotid artery. An echocardiogram showed an ejection fraction of 53% and right ventricular systolic pressure of 88 mmHg, with a negative bubble study and an ischemic pattern of the left ventricular myocardium. The hematology team was consulted on day 3. As the patient was presenting an acute ischemic stroke in the setting of Hb SS disease and hemoglobin on admission was 7.5 g/dL she received 1 unit of packed red blood cells (RBCs). On day 3 the clinical course was complicated by ascending deep vein thrombosis with pulmonary involvement as documented by computed tomography angiography (CTA) in the chest, abdomen, and lower limbs. A thrombophilia screening was performed and an increase in APA values was found with respect to baseline: Lupus anticoagulant (LAC) was detected by Diluted Russell Viper Venom Time (dRVVT); anticardiolipin (aCL) IgG and IgM were respectively 50 GPL/mL by 2.5 GPL/mL and 250 MPL/mL by 15 MPL/mL; IgG and IgM Beta-2-glycoprotein I-1 antibodies (β2GPI-1) were 40 U/mL by 1.5 U/mL and 450 U/mL by 22 U/mL, respectively. In consideration of the new findings, the therapy also included clexane 6000 UI

twice daily (interrupted fondaparinux), methylprednisolone 100 mg twice daily, and gastric protection. On day 4 the patient underwent 4 erythropheresis (ET) procedures using COM.TEC Fresenius cell separator, with Kit PL1. For each procedure performed three days apart from each other, except for the last one performed after a week, about 1200 mL of blood were removed and replaced in two ETs using 3 units, while the other two ETs used 4 units of blood. Fresh leucodepleted blood was used (sampling performed 2/3 days before at most) with HcT 60/62, phenotypically compatible. In each procedure, the exchange was set to arrive at the replacement of the theoretical erythrocyte volume, calculated based on the pre-apheresis hematological values (pre-Hb and pre-HbS). The procedures were well tolerated, and only minor side effects were noted, specifically episodes of hypocalcemia treated with Ca gluconate. Hemoglobin electrophoresis following exchange transfusions revealed 25.5% HbS with a baseline of 42% HbS on the day of admission. She remained alert and oriented. No neurological deficit was noted. On day 22 she was discharged, went home, and was provided with a follow-up appointment at the clinic. Two months after discharge, the patient arrived at the hematology clinic: neurological symptoms have further improved, deep vein thrombosis is resolving as well as pulmonary embolism, and a repeat blood test revealed stable results, including hemoglobin of 9.6 mg/dL, reticulocyte % of 2.95%, lactate dehydrogenase of 188 U, HbS 25% and APA values returned close to normal range, LAC was absent; aCL IgG and IgM were 28 GPL/mL and 50 MPL/mL, respectively; IgG and IgM β2GPI-1 were 35 U/mL and 25 U/mL, respectively (Figure1).

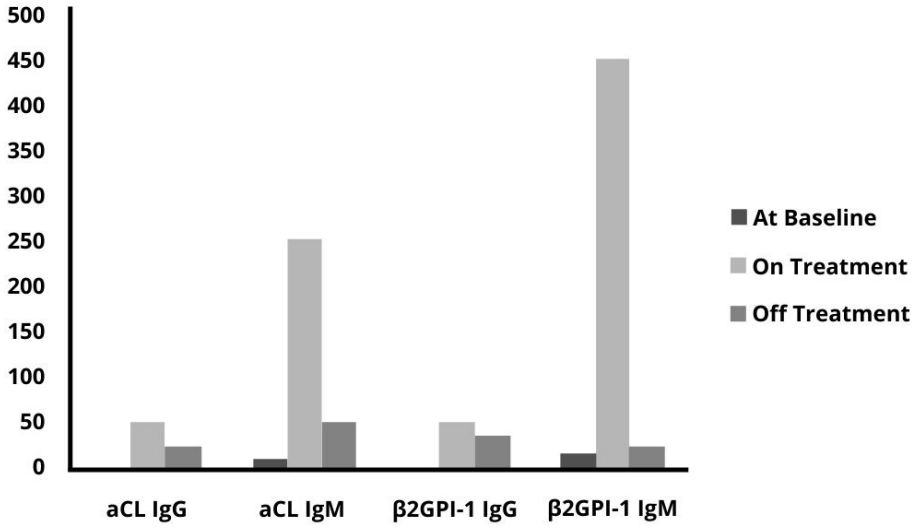

Figure 1. Evolution of changes in anticardiolipin (aCL) IgG and IgM, IgG and IgM Beta-2-glycoprotein I-1 (β2GPI-1) antibodies levels following treatment.

The patient needs neurorehabilitation and continues therapy with cardioaspirin and low molecular weight heparin.

3. Discussion and conclusions

Recent studies strongly suggested that hypercoagulation in SCD is not just a secondary event but contributes directly to the disease pathophysiology [3]. Mechanisms leading to the activation of coagulation are represented by Endothelial and Leukocyte cell Tissue Factor, abnormal activation of thrombin, platelets, and intrinsic coagulation pathway. A few studies have highlighted Circulating Microparticles in SCD patients and these may contribute to thrombin generation by increasing surface phosphatidylserine exposure. Furthermore, anionic phospholipid, including phosphatidylserine, exposure on the surface of erythrocytes occurs during intravascular hemolysis and may induce APA, which supports coagulation activation as a key role in the development of thrombosis in SCD [7]. Several studies showed increased levels of APA in SCD patients, especially with homozygous genotype SS [8]. The finding of increased antiphospholipid antibodies in these patients was compatible with the concept that APA formation was associated with structural changes in the red cell membrane that occur in the red cells of patients with sickle cell disease [9]. Merashli et al. systematic review evaluated the relationship between APA and SCD and revealed a statistical link between APA and SCD, but the clinical relevance of APA in SCD remains unclear [10]. Moreover, SCD patients present a defective activation of the alternate complement pathway linked to the consumption of complement factor B which increases the risk of infection and is thought to predispose to autoimmune diseases [11] such as Systemic Lupus Erythematosus SLE and rheumatoid arthritis RA [12,13]. Aygun et al. showed an immune system overstimulation in SCD patients due to multiple transfusions and chronic inflammation generating clinically relevant auto and alloantibodies [14]. A delayed hemolytic transfusion reaction (DHTR) and hyper-hemolytic syndrome (HHS) are severe complications that can follow red cell transfusions in SCD patients. Free heme, released beyond the "steady-state" intravascular hemolysis, activates complement, and reduced nitric oxide production and anticoagulant protein, facilitating the hypercoagulation state and the immunological disorder [15].

Our case of severe thrombotic complications in a patient with SS-SCD, who showed high APA levels during vascular occlusions treated also with PE, suggests that APA may contribute directly to the SCD pathophysiology, thus a thrombophilic study including detection of APA in patients with hemoglobin SS disease who developed thrombotic complications after presenting with a severe ischemic stroke should be performed. To date, the prothrombotic role of APA in SCD patients requires further investigation.

Declarations

Ethics approval and consent to participate. This manuscript does not report on or involve the use of any animal or human data or tissue.

Conflict of interest

The authors declare no conflict of interest.

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