Thrombolysis After Emergency Cesarean Section in Sickle Cell Disease

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Abstract

Pulmonary embolism (PE) is a rare complication during pregnancy. However, it is still the leading cause of morbidity and mortality. The risk to develop a PE is even higher in patients suffering from an inherited blood disorder like sickle cell disease (SCD). We report on the management of a 28-year-old woman with SCD who was admitted to the hospital with painful sickle cell crisis and developed a massive PE followed by cardiac arrest. The patient could be revived and underwent thrombolysis successfully with recombinant tissue plasminogen activator (r-tPA) 22 h after emergency cesarean section without complications related to thrombolysis. However, she developed an acute kidney injury and transient liver dysfunction which both improved gradually during her course. Finally, she was extubated on the 16th postoperative day and transferred to the obstetric ward on the 21st postoperative day. The patient recovered completely and was discharged home without neurological deficit.

Keywords: Sickle cell disease; Pregnancy; Pulmonary embolism; Thrombolysis

Introduction

Sickle cell disease (SCD) is an inherited autosomal recessive disorder caused by the “sickle” gene resulting in formation of abnormal hemoglobin structure [1]. The term SCD includes sickle cell anemia (HbSS), like in our case, and heterozygous conditions of hemoglobin S (HbS) and other abnormal hemoglobin. The origin of SCD was found in sub-Saharan Africa and the Middle East [2, 3]. Hence the prevalence is high in the Middle East.

Pathophysiologically, the polymerization of the abnormal HbS in low-oxygen conditions leads to the formation of rigid and fragile sickle-shaped red blood cells. These abnormal cells occlude the microvasculature leading to organ ischemia and damage. In addition, the sickle cells are prone to hemolysis due to instability of their membranes. Clinically, this leads to complications like stroke, venous thromboembolism (VTE), pulmonary hypertension and renal dysfunction.

During pregnancy SCD adds on the physiologically adaptive hypercoagulability and increases the risk for perinatal mortality [4, 5], acute painful crisis [6] and thromboembolic events [7].

We report on the management of a 28-year-old pregnant lady with SCD who developed cardiac arrest secondary to pulmonary embolism (PE) 22 h after undergoing an emergency cesarean section.

Case Report

A 28-year-old G2P1 with 33 weeks’ gestation, known case of SCD, was admitted to our hospital in a painful crisis. Obstetric ultrasound on admission presented a single viable intrauterine fetus in breech presentation with the placenta to the posterior away and adequate amniotic fluid volume. Fetal measurements showed: biparietal diameter 33 weeks 2 days, head circumference 33 weeks 1 day, abdominal circumference 32 weeks 4 days, and femur length 32 weeks 6 days confirming the gestational age. The patient had a past medical history of multiple sickle cell crises with exchange transfusions during her previous pregnancy requiring a cesarean section at 33 weeks in 2012. Hereafter the patient received hydroxyurea and contraception. However, she was non-compliant with her medication and escaped from medical follow-up. Likewise, the present pregnancy was without obstetric and hematological monitoring. Beside the SCD no further comorbidities were known.

Based on patient history and her condition the department of hematology and the pain team were involved. After admission to the emergency room an initial management was started by hydration and analgesics. For continuous monitoring the patient was transferred to the High Dependency Unit where cardiotocography (CTG) confirmed fetal viability. The patient responded to the treatment (intravenous (IV) hydration, fentanyl patient-controlled analgesia (PCA)). She was slightly...
tachycardic with 105/min, blood pressure within normal limits, a respiratory rate of 22/min and SpO₂ of 100%. Later on her hemoglobin level dropped from 8.9 g/dL to 7g/dL with an HbS-level of 47%. As the patient was still in pain and the Hb-level dropped nearly two points, a common decision was made by the hematologist and obstetrician to transfuse two packed red blood cells (PRBCs). Meanwhile the patient was hemodynamically stable with good pain relief. The CBC showed leukocytosis for which antibiotic treatment with piperacillin/tazobactam 4.5g IV ter in die (TID) was initiated. On the next day she was complaining about severe, diffuse pain despite ongoing treatment. After a multidisciplinary discussion the decision was taken to perform an exchange transfusion for which the patient was transferred to the surgical intensive care unit (SICU). Here an arterial line was inserted for close monitoring. At the end of the exchange transfusion the patient became tachypneic with a respiratory rate up to 40/min. In addition, B-lines were demonstrated in the basal part of the lung by ultrasound examination as a sign of volume overload or possibility of transfusion-related acute lung injury (TRALI), which is defined as new acute lung injury (ALI) occurring mostly within 6 h after transfusion, which cannot be explained otherwise. Therefore, non-invasive ventilation was started and 20 mg furosemide was given intravenously. Although the urine output was 700 mL over the next 2 h the patient stayed tachypneic with a respiratory rate of around 40/min while her heart rate was 120 - 125 beats per minute (bpm) with a blood pressure of 96/60 mm Hg per minute and SpO₂ 92-95%. The patient’s transthoracic echocardiography revealed a slightly enlarged right ventricle with borderline systolic function. Unfortunately, the CTG-monitoring showed deceleration of the fetus’s heart rate.

Due to the deteriorated state of the mother and the fetus an emergency cesarean section was performed on the next day (day 4) without further complications and minimal blood loss. The delivered baby boy was presented with a weight of 1,725 g. Apgar score 5/8 and pH of 7.25. While the patient was transferred sedated, intubated and ventilated back to the SICU, her newborn was handed over to the pediatrician and admitted to neonate intensive care unit (NICU). To anticipate hemodynamic instability a central venous line and a cardiac output monitor (Pulse Contour Cardiac Output (PICCO)) were inserted to monitor cardiac function, guide volume replacement and catecholamine treatment if necessary. The PICCO system enables monitoring of the patient’s hemodynamic status including the cardiac output, the systemic vascular resistance and the extravascular lung water. At that time the cardiac index (CI) was 4.5 L/min/m², the systemic vascular resistance index (SVRI) was 818 dyne·s/cm²/m² and the extravascular lung water index (EVLWI) was 13 mL/kg. Focused bedside ultrasound investigation demonstrated a slightly enlarged right ventricle, without D-sign, McConnell’s sign or paradoxical interventricular septal movement. As the blood pressure started to drop, norepinephrine infusion in small dose was started. Based on the ultrasound findings of a slightly enlarged right ventricle in combination with increasing hemodynamic instability the suspicion for PE was raised. Therefore, a computed tomography pulmonary angiography (CTPA) was performed showing pulmonary artery embolism in the segmental and subsegmental branches in upper right and lower left pulmonary arteries.

After consultation with hematology heparin infusion was started with a PTT goal of 50 - 70 s. In the next hours the patient developed hematuria and hemoglobin-level dropped from 7.4 to 5 g/dL. For this reason, the heparin infusion was stopped and two PRBC plus six units of platelets were transfused. Unfortunately, the patient’s situation deteriorated during the night necessitating an increased oxygen fraction and noradrenaline infusion rate. A repeated transthoracic echocardiogram (TTE) revealed a rise of right ventricle systolic pressure (RVSP) up to 70 mm Hg, combined with a dilated right ventricle and severely reduced left ventricular preload pointing at ongoing more severe embolic events.

An immediate, multidisciplinary, bedside team meeting was organized and therapeutic options were discussed: surgical removal of the clots, radiological removal and thrombolysis. Unfortunately, a radiologic intervention could not be performed because of technical problems. Moreover, a surgical thrombectomy was not advised because of the diffuse nature of the thrombi in the CT. On the other hand, thrombolysis seemed to be a contraindication shortly after the cesarean section and in the light of the active bleeding. So, the decision was taken not to start thrombolysis unless the situation would not allow to keep the patient’s vital signs acceptable by all conservative means.

About 22 h after cesarean section, the patient developed a cardiac arrest with pulseless electrical activity (PEA). She recovered after two cycles of cardiopulmonary resuscitation (CPR), but the CI dropped to 1.17 L/min/m². During the next 60 min she arrested twice with return of spontaneous circulation (ROSC) after few cycles of CPR each. As a consequence, a decision for thrombolysis with recombinant tissue plasminogen activator (r-tPA) 10 mg bolus followed by 90 mg infusion over 1 h was made.

A few hours later there was a significant improvement in the cardiac index to 3.5 L/min/m², while the central venous pressure decreased to 17 mm Hg with a reduced need for vasopressor support.

Over the following days the patient developed an acute kidney injury requiring hemodialysis and transient liver dysfunction which both were treated accordingly. In neurological review the patient quickly was following commands. A brain CT and later brain magnetic resonance imaging (MRI) were performed which excluded intracranial bleeding and ischemia. The patient was extubated on the 16th postoperative day. Renal and liver functions improved gradually, and the patient could be transferred to the obstetric ward on the 21st postoperative day. Eventually she recovered completely without neurological deficit.

**Discussion**

In the presented case a 33-week pregnant woman with a known SCD was admitted to the hospital showing a clinical picture of painful vaso-occlusive crisis. This complication is the most frequent cause of hospital admission during pregnancy associated with SCD [8]. The coincidence of SCD and pregnancy has a six-fold increased risk in complication rate. In a recent
study 61% of such patients required hospitalization during their pregnancy. The majority needed blood transfusion because of hemolysis. Pulmonary complications and acute chest syndrome (ACS) were in 30% reported which included PE. However, an ACS was the main cause of death in these patients [9]. Beside the recommendation to perform screening for pulmonary hypertension, nephropathy and hepatopathy, what is recommended for SCD patients, the guideline of the Royal College of Obstetricians and Gynecologists [10], gives further information for women with SCD. To reduce the frequency of sickle cell crisis, dehydration, cold, hypoxia, overexertion and stress should be avoided. In pregnancy, dehydration is a relevant risk, because nausea and vomiting occur frequently. The risk of worsening anemia, development of sickle cell crisis, ACS, infection and having a growth-restricted baby with increased likelihood of fetal distress is also increased. Therefore, women with SCD should visit preconceptionally and during pregnancy a sickle cell specialist as part of a multidisciplinary team to give information and guidance on the interplay between pregnancy and SCD. Women should be advised to have a low threshold for seeking medical help during pregnancy.

As recommended in the guideline [10] our patient was assessed and treated by a multidisciplinary team immediately after presentation. After initially positive response to our treatment the patient needed blood transfusion, later exchange transfusion and finally she developed a sequential PE with repetitive cardiac arrests. As a rescue therapy the patient received systemic thrombolysis despite having a high risk of bleeding.

Albeit blood transfusion is the cornerstone in optimizing oxygenation, there is no clear target hemoglobin-level. However, it should be considered in patients with an arterial PaO2 of less than 9.0 kPa on room air and also in less severe dynamic hypoxemia if oxygen requirements are increasing [11].

The patient developed clinical signs suspicious for ACS, a typical complication which is after painful crisis the second most common reason for hospitalization the leading cause for morbidity and mortality in patients with SCD [12].

ACS presents typically with a sudden onset of symptoms of lower respiratory tract illness (e.g., a combination of shortness of breath, retractions, cough) with presentation of new pulmonary infiltrate on the chest radiography. Most commonly it is triggered by an infection but also as a consequence of intrapulmonary aggregates of sickle cells, atelectasis or pulmonary edema [12]. Like in our case ACS often occurs 24 - 72 h after the onset of the painful crisis [13]. It is an acute illness that is characterized by fever and/or respiratory symptoms, accompanied by new pulmonary infiltrates on chest X-ray [14]. As an ACS can be triggered by a pulmonary infection and also PE, both can lead to HbS polymerization. An ACS cannot be distinguished precisely from the clinical presentation of pneumonia. Therefore, it is recommended to treat both diagnoses at the first stage until one or both are confirmed [11]. So, we treated the patient with antibiotics, noninvasive ventilation (NIV) to optimize oxygenation and goal-directed fluid replacement as an integral part of the management of ACS [11]. Broad spectrum antibiotic therapy was initiated because patients with sickle cell anemia have an increased risk of severe bacterial infection, resulting primarily from reduced or absent splenic function due to multiple infarctions [15].

With regard to exchange transfusion recent guidelines on the management of ACS recommend an exchange transfusion for patients who show features of severe disease, in those who deteriorate despite an initial blood transfusion or in those with a hemoglobin concentration higher than 9.0 g/dL [11]. Although some case reports described the use of nitric oxide (NO) in the treatment of ACS [16-18], we considered but decided against the use of inhaled NO as the evidence seems not to be sufficient [19].

Patients suffering from SCD have a higher risk for VTE (pooled odds ratio (OR) 4.4, 95% confidence interval (CI) 2.6 - 7.5, P < 0.001) and PE (pooled OR 3.7, 95% CI 3.6 - 3.8, P < 0.001) when compared to non SCD-patients [20]. This was recently confirmed in another study [21]. The decreased fibrinolytic activity paired with increased procoagulation factors in pregnancy combined with the sickle trait might be responsible for this phenomenon [22, 23]. Unfortunately, D-dimer as a marker for PE is not helpful in our situation because levels are usually elevated during pregnancy [24]. However, imaging with CTPA could proof PE and echocardiography is an important bedside tool. The recent guideline the Royal College of Obstetricians and Gynecologists recommends an urgent performance of a portable echocardiogram or CTPA within the next 60 min after onset of symptoms [25]. There is no contraindication per se regarding CTPA chest in pregnancy. It is a case-to-case decision and should not be withheld if clinically indicated [26]. In general, the diagnosis of PE includes TTE, pulmonary angiography, spiral CT scan, and ventilation-perfusion investigations [27]. However, even if the CTPA is the gold standard for PE diagnosis, in hemodynamically unstable patients, a bedside diagnosis by TTE might be the only available tool. The current European Society of Cardiology (ESC) guidelines [27] recommend to use echocardiography for the decision if primary reperfusion is indicated in clinically unstable patients like in our case. Therapeutic options are thrombolysis; alternatively, surgical embolectomy or catheter-directed treatment based on the location of the thrombus and the local conditions. The measurement of the tricuspid annulus plane systolic excursion (TAPSE) and the presentation of a depressed contractility of the right ventricular (RV) free wall compared with the RV apex (“McConell sign”) are useful bedside echocardiographic parameters in decision making.

In terms of approach intravenous unfractionated heparin is preferred as initial treatment in massive PE with cardiovascular compromise [25]. However, the current ESC guidelines on diagnosis and management of PE mention that if there is an acute RV overload detected by echocardiography in unstable patients the recommended specific treatment is primary reperfusion with thrombolysis, alternatively surgical embolectomy or catheter-directed treatment. In such cases most contraindications for thrombolysis should be considered as “relative” in patients with life-threatening, high-risk PE [27]. However, results regarding bleeding complications are controversial. A meta-analysis showed a higher risk of bleeding if thrombolysis is compared with therapeutic anticoagulation. In patients 65 years and younger, there was no association with major bleeding (OR 1.25, 95% CI 0.50 - 3.14, 2.84% (11/388) vs. 2.27% (9/396)) [28]. This is in agreement with two other studies which could not detect a higher risk of major bleeding or
intracerebral hemorrhage after thrombolysis. These investigations compared heparin plus placebo with heparin plus alteplase [29, 30]. Stein et al demonstrated that the in-hospital mortality attributed to PE was lower in hemodynamically unstable patients who received thrombolytic therapy compared to unstable patients who were not thrombolysed (relative risk (RR) 0.20, 95% CI 0.19 - 0.22, P < 0.0001) [31]. Case reports of perioperative PE treated with systemic thrombolysis with positive outcome and full recovery even with treatable bleeding complications are published [32-35]. Certainly, there might be a bias, because cases with negative outcome might possibly not be published. Luckily, no significant bleeding complications based on the thrombolysis were observed during the further treatment on the ICU or later on the ward and the patient completely recovered.

Conclusions

Patients with SCD are generally in a hypercoagulable state which is even more aggravated by physiological changes during pregnancy. Compared to non-pregnant SCD patients, they carry a higher risk for VTE and PE. The treatment should be based on a multidisciplinary approach following the patient’s course. Decisions should be made in a timely manner based on relevant changes in patient’s state.

In case of a life-threatening PE thrombolysis should not be withheld. In contrast it might be the best suitable option after considering all alternatives. Our case report demonstrates that there is no absolute contraindication for systemic thrombolysis in patients who developed cardiac arrest based on a life-threatening severe PE even shortly after cesarean section.

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None to declare.

Conflict of Interest

None to declare.

Informed Consent

Signed informed consent from the patient to publish her care as a case report was obtained.

Author Contributions

SN wrote the first draft of the manuscript. SR was directly involved in the care of the patient described in the case report and wrote the second draft and completed all edits for revision and submission. MDL provided editing and writing contributions to all sections of the manuscript. SG and EBG reviewed and edited the manuscript. All authors read and approved the final manuscript.

Data Availability

The authors declare that the data supporting the findings of this study are available within the article.

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