TITLE: Sickle cell disease with twin gestation with hypertensive disorder of pregnancy with recurrent crisis and immune hemolysis; A diagnostic and management Enigma

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BACKGROUND: Sickle cell disease (SCD) refers to any of syndromes in which the sickle mutation is co-inherited with a mutation at the other beta globin allele that reduces or abolishes normal beta globin production.The major features are hemolytic anemia,vaso-occlusion, which can lead to acute and chronic pain and tissue ischemia or infarction.These pregnancies are at increased risk of obstetrical and fetal complications,medical complications of SCD are due,to metabolic demands, hypercoagulable state, and vascular stasis associated with pregnancy.

CASE REPORT:22Y old G2A1(MTP) with a history of multiple blood transfusions (12-15) since the age of 12, on hydroxyurea pre-pregnancy, admitted in view of severe anaemia (Hb-5.7) with DCDA twin. Conception was spontaneous with 6 units of blood transfusions in the first trimester.7 units of transfusion were done, but haemoglobin was declining. An extensive workup was done involving a multidisciplinary team. She had a fever episode. Dengue IgM+.4 UNITS of FFP transfusion due to deranged APTT(38.6).She was ANA+, DCT +, HPLC of SCD with Beta Thal trait. On USG, hepatosplenomegaly with hemangioma and gammagandy body in spleen. The immune antibody profile showed a minor blood group antibody. Ecosprin, Enoxaparin,vitcofol and methylprednisolone pulse therapy with antibiotic coverage and blood transfusion was done after complete crossmatch testing minor blood groups. Connective tissue disorder, APLA profile investigations negative. Her haemoglobin was stabilised (HB 6-7). Readmitted at 28 weeks with joint pain. Haemoglobin 3.6 and pulmonary oedema, severe hypertension Dexamethasone,2 units of blood transfusion and 9 units of IVIG transfusion were done along with MgSo4.LSCS was done(30W) with 1 unit of intraop blood transfusion, Hypertension managed with medications and live male and female of 1.235 kg and 1.15 kg were born. Babies are stable in NICU. The patient is stable with post-op haemoglobin of 7.6g/dl and is on hydroxyurea.

CONCLUSION: Early identification of SCD women with twin pregnancy with vigilant surveillance, well-defined care plan and extensive collaboration with multidisciplinary team highlights the advantage of improved clinical outcomes in complicated cases.

INTRODUCTION

The sickle point mutation in the beta-globin gene results in the production of sickle haemoglobin, which is less soluble than normal fetal or adult haemoglobin. Sickle cell disease (SCD) refers to any one of the syndromes in which the sickle mutation is co-inherited with a mutation at the other beta globin allele that reduces or abolishes normal beta-globin production. These include sickle cell anaemia (homozygous sickle mutation), sickle-beta thalassemia, haemoglobin SC disease, and others.[1,2]

The clinical manifestations of SCD are protean. The major features are related to hemolytic anaemia and vaso-occlusion, which can lead to acute and chronic pain and tissue ischemia or infarction. Splenic infarction leads to functional hyposplenism early in life, which in turn increases the risk of infection. These complications have a major impact on morbidity and mortality. As a general rule, individuals with sickle cell anaemia (homozygous HbS) and sickle-beta0-thalassemia have more severe manifestations than those with haemoglobin SC disease or sickle-beta+-thalassemia

Most pregnancies complicated by maternal sickle cell disease (SCD) are likely to result in a live birth, these pregnancies are at increased risk of obstetrical and fetal complications, as well as medical complications of SCD [3-6]. These risks are due, at least in part, to the metabolic demands, hypercoagulable state, and vascular stasis associated with pregnancy. Access to a multidisciplinary care team knowledgeable about sickle cell disease and high-risk obstetrics can significantly decrease morbidity and mortality.

CASE PRESENTATION:Our patient, a 26 year G2A1 with DCDA TWIN pregnancy at 17W+6D period of gestation(POG) presented to OPD on 12.6.21 for routine ANC with history of joint pain a month ago and 1 unit of PRBC transfusion 3 days back in an outside hospital. She was admitted for evaluation and further management. On admission, she was afebrile and vitally stable. Routine investigations were sent and she was started on conservative management. She had a history of sickle cell crisis episode presenting with joint pains and 6 units of blood transfusion in a private hospital one month ago at 3-4 month POG. The patient was diagnosed with sickle cell disorder at age of 12 years and had a history of blood transfusion once or twice each year in view of severe anaemia with an average of 1.2 times transfusion each year. She also had a history of ICU admission in 20212. Her father was a known case of sickle cell trait and her mother was sickling negative. The patient was on hydroxyurea and had MTP done 8 months ago at 2-month POG in an outside hospital.Present pregnancy was planned and spontaneous. she had stopped hydroxyurea intake 1 month preconceptionally and was following up in a private hospital.

Her preliminary lab investigation showed that she had severe anaemia with Hb 5.7 Hb and TSH was mildly elevated. (3.28) and anti-TPO AT 191 .2 unit PRBC transfusion was done and antibiotic coverage with ceftriaxone along with conservative management and tab methylcobalamin 1200mg/ day regimen was initiated. General medicine,hemato-oncologist & endocrinology opinion was taken. She was started on tab Thyroxine 50 mcg OD and was planned

for vaccination post-delivery.Post BT her haemoglobin (HB) was 7.5 mg/dl.She was transfused with one unit of PRBC again and the dose of thyroxine was increased to 62.5 mcg thyroxine in view of raised TSH of 7.6. Post BT her HB was surprisingly 7.4mg/dl. Tab Ecospirin 150 mg OD and enoxaparin 0.6 ml SC was started.

USG whole abdomen was done which showed hepatosplenomegaly with hemangioma of size 1.9x2.1 cm in segment 2 of liver and gammagandy body in spleen.USG detailed anomaly scan showed no obvious congenital anomaly in the fetus with normal doppler study.

HPLC showed SCT with Beta thal trait minor and repeat CBC after 2 days showed HB of 6.7.She was further screened for antibodies by ICT, DCT and ANA profile. Parvovirus infection screening was also done. Urgent hemato-oncologist and General physician opinions were taken in view of falling HB level after recurrent transfusion. She was planned for blood transfusion to keep target HB to 8g/dl and investigations were sent to rule out hemolysis along with a faecal occult blood test.

Her ANA was positive(ANA HEP2+, Ro52+AMA ug+)ICT negative and DCT was weakly positive faecal occult blood test was negative. Her retic count was 9.24%(corrected retic count was3.9%)Her antibody screen and repeat DCT, ICT and HPLC was done. She was found to be minor blood group antibody positive and repeat ICT was weakly positive(equivocal). Clinical tests for connective tissue disorder were negative.

Blood transfusion with leukoreduced RBC and after possible complete cross-matching of blood for minor blood group antigens was done. Her APLA profile was negative done after stopping LMWH for 3 days.PNH screening was also negative.

The patient had a fever episode of high grade(102F)two weeks after admission. The fever persisted for 3 days.Her fever profile showed her to be Dengue Ns1Ag positive and Blood culture sensitivity was MRSA+.

Her antibiotics were upgraded and she was started on injection PIPTAZ and was transfused with 4 units of FFP in view of slightly increased APTT(38.6). There were no further fever episodes. Pulse therapy of injection methylprednisolone followed by tab prednisolone at 0.5 mg/kg(30 mg) was started after neonatology clearance.

Methylprednisolone seemed to be effective and her Hb seemed to be stabilised between 6-7g/dl over 1-week observation. During this course, the patient was transfused with a total of 8 units of PRBC and 4 units of FFP(IPD stay of 1.5 months). The patient was discharged on tab predinisolone 30 mg OD along with LMWH & Ecospirin.

The patient presented again in the Emergency department around 1.5 months after discharge at 27W+6 D POG with complaints of joint pain. She was readmitted and her HB was 3.6 g/dl.Dexa coverage was done along with management of the Sickle cell crisis episode. she also developed Severe PE with premonitory symptoms.2 units of PRBC Transfusion was done along with MGSO4 neuroprotection .9 units of IVIG transfusion was done and the patient was taken for EMERGENCY LSCS at 30W POG I/v/o of severe PE with a Twin pregnancy and Sickle cell disease with beta thal minor and minor blood group antibody positivity with severe anemia.1 unit of PRBC transfusion was done intraop. Preterm alive twins (male & female) were delivered of 1.1

kg and 1.2 kg. Both the babies are stable on room air and on breastmilk and are presently in NICU in view of prematurity. The patient has been restarted on Hydroxyurea.She is presently stable on 7.6 HB Post OP

DISCUSSION: Twin pregnancy in the presence of sickle cell disease poses a significant risk both to the mother and fetus. Transfusion remains challenging in women with twin pregnancies and SCD. A 2013 Cochrane review on prophylactic versus selective blood transfusion for SCD in pregnancy [7] found only one study, Koshy et al. 1988 [8], to include in its analysis. This was a small study with only 72 women included of which four were twin pregnancies. Although the study acknowledged that twin pregnancies were at higher risk of complications of pregnancy, it noted that prophylactic transfusion did not appear to reduce the incidence of complications. In the above case 26y G2A1 patient presented with DCDA twin pregnancy with multiple sickling crises and severe anaemia. She was transfused with 8 units of PRBC in our institution but her HB level was in a declining trend after 2-3 days after each transfusion. To add to further complication she had febrile episodes with dengue IGM+ and MRSA positive blood culture. Her immune antibody profile showed her to minor blood group antibody positivity and ANA+. Her USG was peculiar as it showed hepatosplenomegaly rather than hepatosplenomegaly as commonly seen in sickle cell diseased patients. Multidisciplinary team involvement was done and it was theorized that recurrent blood transfusion leading to a declining HB trend was due to splenic sequestration and alloantibodies developed in the patient due to recurrent blood transfusion leading to immune hemolytic anaemia. Methylprednisolone therapy along with proper antibiotic coverage seemed beneficial and stabilised patient's HB between6-7 g/dl.At around 28 weeks, she developed crisis episodes again with severe PE and IVIG transfusion was tried along with completely cross-matched blood transfusion.The patient delivered twin live male and female babies at around 30w POG by C-Section. Both babies are stable on room air in NICU in view of prematurity.The patient seems to maintain stable HB between 6-7 g/dl and has been restarted on hydroxyurea therapy.

CONCLUSION: Our case highlights the advantage of closer monitoring and comprehensive multidisciplinary care in delivering improved clinical outcomes. In our patient, recurrent severe anaemia occurred probably due to splenic sequestration and immune hemolysis due to uncommon presentation of sickle cell disease with hepatosplenomegaly and minor blood group antigen positivity. Methylprednisolone therapy along with IVIG TRANSFUSION in our case of sickle cell disease with beta Thal minor and minor blood group antibody positivity presenting multiple crisis episodes seems to have worked well.

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