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Pregnancy with Severe Anaemia and Pulmonary Hypertension: A Presentation of Hb E –ß Thalassemia

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Summary:

The interaction of HbE with ß-thalassaemia results in HbE-ß-thalassaemia, an extremely heterogeneous clinical condition. HbE-ß-thalassaemia is the most common form of ß-thalassaemia in Southeast Asia and accounts for approximately 50% of cases of transfusion –dependent cases of haemolytic anaemia. Still an undiagnosed population exist in our midst often presenting with complications of chronic haemolysis along with anaemia. Obstetricians are further perplexed while managing these patients in pregnancy with added foetal risks. Pulmonary hypertension, cardiac arrhythmia, systemic iron overload from chronic blood transfusion usually evolves from the disease itself.The risk of the foetus inheriting the trait of either ²-thalassemia or Hb-E exists(25% in each pregnancy) along the possibility of being homozygous for this disorder if the father bears the carrier status(25 % in each pregnancy) cannot be overlooked. Here we report a 20-year old primigravida with Hb E- ß thalassemia presenting at 40 weeks of pregnancy with severe anaemia (4 gm/dl) and respiratory distress. The patient also had hepatosplenomegaly and cholelithiasis. The patient had remained undiagnosed upto the time of presentation and had remarkably received no blood transfusion since childhood despite the history of recurrent jaundice. The patient was further investigated and found to have moderate pulmonary hypertension and mild tricuspid regurgitation. After correction of her anaemia and supportive cardiac care, she delivered a male child of 2.75kg by caesarean section. Her cardiac condition also significantly improved after delivery.

Key words: Thalassemia, Hb E-â thalassemia, pregnancy, pulmonary hypertension.

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Introduction:

Thalassemia is among the most common monogenetic disorder worldwide.Among the variants of Haemoglobinopathies, Haemoglobin E- beta thalassemia closely resembles ²- thalassemia major with its long-term sequels, producing transfusion - dependent anaemia. Therefore, a microcytic hypochromic blood picture with evidence of haemolysis along with MCH less than 80fL and MCHC less than 28 pg mandates Haemoglobin electrophoresis for confirmation of the Haemoglobin variant.Haemoglobin electrophoresis is the gold standard for confirming Hb E-² thalassemia.[1]Still a large undiagnosed burden of thalassemia lurks in our society and they present for the first time in pregnancy with features of complications of chronic haemolysis/ anaemia, due to the high adolescent pregnancy rate in our country. Screening for haemolytic anaemia during antenatal booking is not a routine practise. Recent epidemiologicalsurvey published by Thalassemia International Foundation (TIF) shows that Bangladesh is among one of the most highly affected country with haemoglobin disorder in Asia with the carrier and frequency rates: Thalassaemia Trait – 4.1 %,Haemoglobin E trait – 6.1 %, Anticipated new affected births annually: 6435 based on carrier rate, population size and other demographic indices and Living patient with thalassaemia – 50000 to 60000.[2]Hepatosplenomegaly, cholelithiasis and pulmonary arterial hypertension (PAH), conduction defects/arrhythmia and/or cardiomyopathy due to hemosiderosis may evolve with time. Thorough cardiac evaluation which includes an echocardiography is part of the obstetric care package in patients suffering from chronic haemolysis. In this context, pulmonary hypertension is one of the leading causes of morbidity,

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though there is very limited data related to the prevalence and impact of PAH associated with haemolytic disorders in the developing world.[3]

Case report:

A 20- year old primigravid patient, hailing from Sylhet presented at 40 weeks 4 days of pregnancy with generalized oedema, exertional dyspnoea and shortness of breath at rest for one month and dry cough for 2 days. She was on infrequent antenatal check-up. After a quite unremarkable antenatal periodat 39th week of gestation, she was detected to be hypertensive with no associated proteinuria and was on Tab ±-Methyl–dopa (250 mg) twice daily. Family history revealed that her elder sister died during pregnancy at term due to dyspnoea and suspected heart failure. Her father died of blood cancer. She is third among 4 sisters and 2 brothers, none of whom have been subjected to any screening procedures. From childhood she suffered from repeated episodes of jaundice but was never evaluated/ diagnosed.She had never received blood transfusion. Examination revealed severe anaemia, facial features: malar prominence with facial puffiness, marked bipedal and sacral oedema and bilateral basal crepitations. The obstetric examination revealed foetal growth corresponding to the gestational age and average liquor volume and reactive CTG(cardio-tocopgraph). Collaborative consultation was done with internal medicine and cardiologists and they suggested the following investigations which revealed: Haemoglobin % 4.41 gm/dl at admission, MCV 67.8fL, MCH 19.4 pg, MCHC 28.7 gm/dl, RDW (Distribution of reticulocyte width) 31.7%, PBF (Peripheral blood film): Haemolytic anaemia with neutrophilic leucocytosis. ANA(Anti-nuclear antibody) negative, Haemoglobin electrophoresis: Hb F 34.6%, Hb E 60 % and Hb A_2 5.2%. Comment: Hb E/^{20} thalassemia (As no Hb A).Serum Ferritin 90.2 ng/ml, Bilirubin Total 1.4 mg/dl,Direct 0.58 mg/dl, Indirect 0.82 mg/dl, LDH1,863U/L (normal value 230-460 U/L),Uric acid 8.8 mg/dl (normal value 2.4-5.7 mg/dl), Urine R/M/E and C/S: Plenty of pus cell with Enterococcus colony count > 10^5/ml, resistant to all cephalosporin.

Ultrasonography of the whole abdomen revealed moderate hepatosplenomegaly with homogenous parenchyma withcholelithiasis, normalpancreatic outline with uniform tissue character. Spleen: moderately enlarged 170x78 mm, dilated portal vein 13mm along with 36^+ weeks gravid uterus. ECG showed sinus tachycardia with ST- T abnormality and poor progression of R wave in V_1-V_3. Echocardiography performed on the day of admission revealed mild pericardial effusion (6mm), Left Atrium and Left Ventricle are dilated; other chamber dimensions are normal, mild Tricuspid Regurgitation with moderate pulmonary hypertension (RVSP right ventricular systolic pressure 55.1 mm Hg) with good left ventricular systolic function (EF 55% at rest).The patient was managed according to the advice of the internal medicine specialists and cardiologist. She received Inj. Frusemide 160mg I/V 12 hourly after admission for the management of pulmonary congestion/heart failure. The anaemia was corrected with 4 units of packed cell transfusion to 10.7 gm/dl. The patient received nebulisation with Salbutamol 6 hourly, Inj. Meropenem for cystitis. Foetal monitoring with CTG (cardio-tocography) was reactive. As her symptoms improved with supportive care, Lower uterine caesarean section (LUCS) was performed three days after admission. She delivered a 2.75 kg male child with good APGAR score. She had a normal post-operative convalescence and was discharged on the 6th post-natal day. Echocardiography repeated in the post-partum state showed moderate reduction of the pulmonary hypertension (RVSP 35.4mm of Hg). The patient was prescribed tablet Ambrisentan 5 mg once daily after delivery by the cardiologist. The patient was advised to maintain contact with cardiologist and medicine specialist. She was also advised to have cholecystectomy for cholelithiasis and seek surgical opinion regarding necessity of splenectomy.

Discussion:

Pulmonary arterial hypertension (PAH) is a chronic progressive disease of the pulmonary vasculature, characterized by elevated pulmonary arterial pressure and secondary right ventricular failure.The estimated incidence of secondary pulmonary hypertension is 1case per 272,000 persons. About 1,000 new cases of pulmonary arterial hypertension are diagnosed each year in the US. Pulmonary hypertension is more common in women than in men (ratio: 1.7 to 1).[2]The non-specific nature of symptoms such as dyspnoea, fatigue, syncope, dizziness, palpitations, orthopnoea and chest pain associated with PH also mimic those of

moderate to severe anaemia, as in this case.[3,4] The progression and reversibility of pulmonary hypertension depend on the nature of the pulmonary vascular lesion and the aetiology. Chronic haemolytic anaemia has been placed in the Dana point 2008 updated clinical classification as an associated condition (1.4.6) [4,5]rendering it to be responsible for this clinical presentation in this case.

Retrospective studies have reported that 10- 75 % of patients with thalassemia have elevated pulmonary artery systolic pressure (PASP).[6,7]Our case suffered from moderate to severe PAH during pregnancy. Compared with normal patients, the rate ratio for death for moderate PAH and severe PAH was4.4 and 10.6 respectively.[8] Prospective study of outcome of patients with thalassemia major/sickle cell trait revealed that 14 % of patients with PAH and 2% of patients without PAH died during a 2- year follow-up period, defining PAH to be an independent risk factor for mortality. [9]

A study by Weiss et al demonstrated a 30% to 50% mortality rate of pregnancy complicated by primary PAH. According to current guidelines, pregnancy should be avoided or terminated early to reduce stress in women with PAH. [10]But in undiagnosed cases of PAH presenting for the first time in advanced pregnancy as in our case, the management must be individualized and outcome carefully guarded.

The pathogenesis of PH in haemolytic disorder is multifactorial.[11] The central risk factor is haemolysis. Free Haemoglobin inactivates Nitric oxide NO (the intrinsic vasodilator) and releases arginase, which depletes L- Arginine, the substrate of NO synthesis. Phosphatidyl serine released from lysed RBC micro-vesicles activates micro-thrombosis and enhances red cell adhesion to endothelin in the pulmonary vasculature, thereby inducing fibrotic parenchymal change, resulting in PAH.[12]Here Ambrisentan acts as anEndothelin receptor antagonist and gradually improves symptoms of exertional dyspnoea.However, it is highly teratogenic and therefore contraindicated in pregnancy.[13,14] Our patient considerably improved post-partum with supportive care and this specific therapy.

Conclusion:

Pregnancy with unexplained anaemia with shortness of breath should be carefully evaluated and regarded as a high-risk pregnancy, particularly at term.The probabilities of cardiac cause, haematologic dyscrasia and SLE should be excluded and the patient should be dealt by a multidisciplinary team to optimize outcome and ensure comprehensive management. Since advanced pulmonary hypertension is less responsive to therapy, early identification and management of pulmonary hypertension is recommended.The awareness of Thalassemia and its implications on the carrying female can help to prevent the spread of an autosomal recessive disease pattern in our community; thereby contribute to a future healthier generation.

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