Tricuspid regurgitant velocity elevation in a three-year old child with sickle cell anemia and recurrent acute chest syndromes reversed not by hydroxyurea but by bone marrow transplantation

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Abstract

Elevated Tricuspid Regurgitant Velocity (TRV) has been related to higher mortality in adults and to hemolysis, lower oxygen saturation during 6-minute walk test and acute chest syndrome (ACS) in children with sickle cell disease (SCD). Hydroxyurea (HU) has reduced TRV value in children and adults. We describe a three year old HbSS child with recurrent ACS -resulting in lung hypoperfusion-, mild hemolysis and TRV elevation since age two. He did not improve after HU treatment but 1 year after undergoing BMT from an HbAA HLA-related sibling, presents no signs of hemolysis and normal TRV, although lung damage remained.

Case Report

A 21-months Nigerian male was diagnosed with HbSS in occasion of the first ACS presenting with infiltration in the left lung and pleural effusion. At 23 and 26 months he experienced a second and third ACS with infiltration of the left lobe. Steady state hematological parameters are shown in Table 1, while steady state Blood Pressure (BP) and SatO2 were above the 90th percentile and 97-98%, respectively. Steady state TRV at 28 months was 2.8 m/sec. At 30 months he began HU 10 mg/kg, gradually increased to 30 mg/kg in four months. The treatment was well tolerated. At 42 months, 1 year after starting HU, despite improvement of hematological parameters, TRV was still 2.82 m/sec. BP had dropped to normal values. ECG and cardiac ultrasound (including Tissue Doppler) at 21, 38 and 43 months were normal. He never presented with obstructive sleep apnea or asthma. Transcranial Doppler (TCD) velocities remained conditional before HU and after HU -time averaged mean velocity of maximum blood flow (TAMM) of 185 cm/sec and 189 cm/sec, respectively. Having experienced recurrent ACS and persistent high conditional velocities on TCD, due to availability of an HbAA HLA- matched sibling he was offered BMT.

As part of the BMT work-up he underwent lung CT scan showing numerous perilobar strie dense in the lower left lobe, with increased density of the parenchyma, interpreted as lungs scars due to the recurrent ACS, and pulmonary perfusion scintigraphy revealing hypoperfusion of the entire left lung, mainly of the lower lobe respectively (Figure 1).

At 47 months he received BMT with the following conditioning regimen: Thiopeta 8 mg/kg/day (70 mg x2 times on day -7), Treosulfan 14 g/m2/day (9.8 gr on day -6, -5 and -4), Fludarabine 40 mg/m2/day (28 mg on day -6, -5, -4 e -3), antithymocyte globulin 175 mg/day (on day -4 and -2). Polymorphonucleated leukocytes and platelet engraftment occurred at day +20 and +22 respectively. No transplant related complications were observed.

One year after BMT he presents with 100% chimerism, no HbS on electrophoresis and is currently well, having experienced no SCD-related complications. Hematological and bio-
chemical values are within normal range for age (Table 1) and TRV dropped to 2.01 m/sec. A pulmonary perfusion scintigraphy performed 1 year after BMT still shows persistence of hypoperfusion of the left lung (unchanged from pre-BMT perfusion scintigraphy).

Discussion

Our case represents, to our knowledge, the first reported case of a very young SCD child with TRV elevation that did not reduce after HU treatment, but normalized after BMT.

Several factors contribute to the increase in TRV in SCD children, including increased pulmonary flow volume (cardiac output), increased left ventricular filling pressures, increased blood viscosity, and increased pulmonary vascular resistance.8 SCD children can also experience systemic hypertension, left-sided volume overload, and abnormal diastolic function, all of which lead to elevated left ventricular filling pressures and secondary elevation of pulmonary artery pressures. Our patient had surely several of the above mentioned factors.

The lack of response of TRV values to HU has been described in only one older patient with severe PH12 and HU efficacy in reducing TRV values is still open. In fact, while some studies demonstrated the protective effect of HU on the development of PH in adults12 and children,11 others have not and HU-induced high haemoglobin F levels have, on the contrary, been related to higher TRV velocities.13 HU has reversed Doppler-defined PH in SCD children14 and adults12 probably due to the combined reduction of hemolysis and red cell adhesion, and to the improvement of vascular function,14 even when the increase in haemoglobin concentration was modest (from 8.3 to 8.7 g/dL and from 7.52 to 7.98 g/dL).11,12 But HU was not effective in reducing TRV in our patient, despite the increase in Hb level (from 7.08 to 8.1 g/dL), the significant increase of HbF% and the reduction of hematologic parameters related to hemolysis (reticulocytes, AST) and to blood viscosity (platelets, white blood cells). Additive effect during HU treatment was not effective in reducing TRV in our patient, although Hb levels were substantially increased (from 8.01 to 12.3 g/dL), and to the improvement of vascular function. In fact, while HU reduces hemolysis, reduces adhesion molecules (on red cells, platelets, WBC and vascular endothelium) and seems to improve vascular tone14 while displaying controversial effects on inflammation,20 BMT, especially if a BMT with HbAA donor-eliminates hemolysis and inflammation, improves rheological characteristics and determines substantial vascular repair with restoration of the endothelial lining and maintenance of vascular homeostasis.21 Under the umbrella of Doppler-defined PH probably fall different subgroup of patients in which the various pathogenetic events (hemolysis, oxidant stress, inflammatory stress, chronic thromboembolism, in situ thrombosis, chronic hypoxemia with activation of proliferative mediators, parenchymal and vascular injury) may be differently involved and may require different therapeutic approaches.6,20,22 In very young patients, TRV elevation might express a biomarker of disease severity and systemic vasculopathy5 instead of true PH and only prospective trials evaluating pulmonary vascular resistance could aid in clarifying this issue.

Nevertheless, our case shows that TRV reduction in young patients, having experienced recurrent ACS with mild hemolysis and persistent TRV elevation resistant to HU treatment, can be a positive concomitant effect of BMT.

References