Remission of Microangiopathy in Transplanted Thalassemic Child

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Abstract Transplant associated thrombotic microangiopathy is a severe complication of Hematopoietic stem cell transplantation. Although there is agreement in terms of diagnostic criteria, treatment options are not clarified yet. We present a patient aged 2.6 years who developed transplant associated thrombotic microangiopathy after allogeneic bone marrow transplantation and to discuss both risk factors and possible spontaneous remission of transplant associated thrombotic microangiopathy.

Keywords Transplantation · Microangiopathy · Cyclosporine · CMV infection

Introduction

The transplant associated thrombotic microangiopathy (TAM) is a multi-organ disease primarily affecting kidneys and central nervous system and represents an important cause of morbidity and mortality after stem cell transplant [1]. Post-transplant TAM is probably due to the presence of a great amount of microaggregates of ultra large von willebrand factors (ULvWFs) in the microcirculation and consequent hemolytic anemia and organ damage. Many factors can contribute to TAM onset, such as severe GVHD, infection (fungal, viral) or the use of cyclosporine a (CSA) or Tacrolimus, all conditions which can result in

severe endothelial damage and extensive generation of ULvWFs in the microcirculation [1, 2].

The TAM usually occurs within the first 100 days after stem cell transplantation and is often associated with adult recipient age, female sex, unrelated or HLA-mismatched donor grafts, GVHD [2]. The incidence of TAM is variable, depending on the diagnostic difficulty, and varies 6–12 % after allogeneic transplantation and 1–5 % after autologous transplantation [3–8] with mortality rates as high as 30–50 %.

Case Report

A 2.6 years old female patient diagnosed with Thalassemia major underwent allogeneic bone marrow transplantation from fully HLA-matched sibling donor. Before transplantation both donor and patient had positive CMV IgG antibody titre, but negative IgM titres. The conditioning regimen consisted of oral Busulfan 14 mg/kg for 4 days, Thiotepea 10 mg/kg for 1 day and Cyclophosphamide 200 mg/kg for 4 days.

Short course Methotrexate and CSA were given for the prophylaxis of GVHD. Neutrophil and Platelet engraftment occurred on days +16 and +18 post transplant respectively. Since day +37 to day +39 and in absence of any signs of a-GVHD there was a significant drop in the absolute platelet count [from 80,000 to 25,000] accompanied by a gradual fall in hemoglobin level [from 8.5 to 7.8 gms/dL] and increasing reticulocyte count [3.5 %]. plasma lactate dehydrogenase [LDH] level was elevated [1260] [Fig 1].

Direct Coombs test was negative. Peripheral blood smear revealed anisocytosis, poikilocytosis and few schistocytes [2 %]. On the basis of these results TAM was diagnosed.

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Fig. 1 Correspondence

Concomitant CMV reactivation was detected [CMV copies were 2080 mL] and intravenous Gancyclovir treatment was started immediately. CSA dose was reduced to one-third based on its possible pathogenetic role in TAM and Mycophenolate mofetil was added as immunosuppressant. CMV copies reduced to <600 mL on day +48 and Gancyclovir therapy was ceased on day +73 after three consecutive negative CMV PCR results. A dramatic improvement in LDH levels down to 476 and reticulocytes count to 2.2 % with spontaneous and gradual improvement in platelets count and Hb level up to day +54 were recorded [Fig 1].

On day +87 there was a transient impairment of hematopoiesis with Hb level down to 8 gms/dl and platelet count down to 87,000. This was attributed to Mycophenolate which was discontinued and substituted with CSA at standard dosage, this was associated with normalization of hematologic values. Hematopoiesis as well as chimerism remained stable at day +180 post transplant with no clinical suggestion of TAM recurrence.

Discussion

The current case report suggests that a timely and early diagnosis of TAM may allow to successfully manage this severe complication with so called TAM precautions only.

According to recent literature data [1, 9] the principal criteria for diagnosis of Microangiopathy are:

- Lactate dehydrogenase >600 IU/L, b) blood smear Schistocytes >25 (sometimes with contemporary

presence of erythroblast cells), c) Reticulocytes count >20 × 1000 L, d) fast and unexplained drop of Platelets count in patients with previous stable value of platelets and in absence of disseminated intravascular coagulation, e) fast and unexplained drop of hemoglobin level and in the absence of severe hemorrhagic disease, f) progressive renal insufficiency and/or neurologic signs as confusion, blurred vision and seizures (in few cases only).

Due to non- availability of Defibrotide, a drug possibly effective in the treatment of TAM [10] and keeping in mind CMV reactivation and/or CSA as suspected causes of TAM we had no management option other than optimizing CMV treatment, decreasing CSA dose and introducing Mycophenolate mofetil for GVHD prophylaxis. These measures resulted in favourable outcome most probably because there was no associated GVHD.

Some authors are in favour of complete stopping of medications such as CSA, Tacrolimus and Sirolimus as soon as TAM is diagnosed [3, 4] but no reliable data have supported this suggestion [2]. Notably in our patient resumption of full dose CSA did not result in TAM relapse.

Some centres employed plasma exchange as part of the management of TAM but response rate has been disappointing in this setting [10] while favourable results have been shown in idiopathic Microangiopathy only [10, 11].

Daclizumab and Rituximab [12, 13] have been recently used with some success in few cases possibly by virtue of their role in controlling GVHD and consequently TAM. Subsequent severe immunosuppression, however, resulted in life threatening infectious diseases.

Our patient did not receive any cryosupernate/plasma exchange/plasma infusion/rituximab after diagnosis of TAM.

Considering the effectiveness of Defibrotide (Procyclide) which acts as an anti thrombotic and fibrinolytic drug in post transplant veno-occlusive disease [14, 15] pathogenesis related to endothelial damage, we are in favour of this drug for post transplant TAM as claimed by some authors [2, 15–17].

In conclusion, though there is no consensus in the treatment of post transplant TAM and in the impossibility to use Defibrotide, we would like to report this fortunate outcome in a patient with TAM and concomitant CMV infection managed early and without defibrotide.

In the near future, multi- centre prospective or retrospective studies are needed to confirm conclusive treatment regime for a post transplant recovery of TAM using various available options.

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