A Case of Transplantation-Associated Thrombotic Microangiopathy with Cardiac Involvement Successfully Treated with Plasma Exchange

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Abstract Transplantation-associated thrombotic microangiopathy (TA-TMA) is occasionally described as a serious complication after allogeneic and, more rarely, autologous stem cell transplantation (SCT). It is characterized by poor outcome with high mortality rate. Plasma exchange (PE) has been reported as successful first-line therapy in other thrombotic microangiopathies. However, unlike to idiopathic forms, response to PE are usually suboptimal in TA-TMA and the use of PE remains controversial, because the exact mechanism of injury is not yet understood. The kidney is the most commonly affected organ and injury has rarely been reported elsewhere in the body, such as in lungs and gastrointestinal tract. Although several case reports have documented myocardial infarctions in patients presenting classic thrombotic thrombocytopenic purpura (TTP), there are no reports documenting cardiac involvement in TA-TMA. We describe a case of a 66-year-old man who experienced TA-TMA accompanied by cardiac ischemia after autologous SCT for multiple myeloma, successfully treated with PE. The immediate start of PE induced a complete remission of TA-TMA and disappearance of cardiac ischemic signs and symptoms except of a residual chronic renal failure.

Keywords Autologous stem cell transplantation · Transplantation-associated thrombotic microangiopathy · Plasma exchange · Cardiac ischemia

Introduction

Transplantation-associated thrombotic microangiopathy (TA-TMA) is a rare but potentially devastating complication of hematopoietic stem cell transplantation (HSCT) that can occur after autologous or allogeneic HSCT. TA-TMA belongs to the family of thrombotic microangiopathies like haemolytic uremic syndrome (HUS) and thrombotic thrombocytopenic purpura (TTP).

Although endothelial injury represents the final common pathway of the disease, the exact pathophysiology of TA-TMA remains unclear and there are no widely accepted criteria for the definition of TA-TMA, despite being first recognized more than three decades ago.

Recent case reports have identified the involvement of different organs besides the kidney, like the lungs and gastrointestinal tract. Despite previous studies have concluded that plasma exchange (PE) is less effective in the treatment of TA-TMA compared to TTP, several recent reports have shown the benefit of early PE initiation in TA-TMA.

We describe a case of TA-TMA with cardiac ischemia occurring after autologous SCT in a patient with multiple myeloma successfully treated with PE.

Case Presentation

In March 2011, a 66-year-old man was diagnosed with MM IgA Kappa (Stage Salmon-Durie IIA, International Staging

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System II) and treated with three courses of Thalidomide-Dexamethasone obtaining a partial response, then with three consecutive courses of cyclophosphamide at intermediate dosage followed by hematopoietic stem cell harvest after the second and third cycle. In January 2012, he received conditioning chemotherapy with melphalan 100 mg/m^2 and consequent autologous SCT of a total of $2.36 \times 10^6/\text{kg}$ CD34+ cells. On day 9 post-transplant he experienced an atrial fibrillation with high ventricular response treated with intravenous amiodarone and resulting in a return to sinus rhythm after 24 h. On day 10 he was treated with intravenous foscarnet sodium for cytomegalovirus (CMV) reactivation, demonstrated by an increase of plasmatic CMV DNAemia copies detected by polymerase-chain reaction (PCR). On day 19, the patient revealed left arm pain. Vital signs were normal, physical examination showed petechiae on the lower limbs and scleral jaundice. His blood tests showed an increase of I-troponin (2.11 ng/ml , normal value $<0.05 \text{ ng/ml}$) with normal level of CK-MB and myoglobin. The electrocardiogram showed T-wave flattening in inferior-lateral area. Other blood exams revealed a falling platelet count from $43 \times 10^9/\text{L}$ the day before to $16 \times 10^9/\text{L}$ and a falling in haemoglobin levels (from 8.2 to 7.1 g/dl). Blood chemistry revealed hemolysis: total bilirubine 2 mg/dl with indirect bilirubine 1.77 mg/dl ; lactate dehydrogenase $1,611 \text{ U/L}$; increased of reticulocytes count; reduction in haptoglobin levels and renal impairment (creatinine 1.65 mg/dl , urea 69 mg/dl). Coagulation parameters were normal. Blood smear examination showed the presence of 6 % of schistocytes.

CMV Dnaemia and Blood Cultures Were Negative

According to the proposed criteria of International Working Group [1] and of the blood and marrow transplant clinical trials network (BMT CTN) [2], a diagnosis of TA-TMA was made and, at the same time, it was made the diagnosis of acute coronary syndrome treated with oxygen therapy and continuous infusion of nitrates, obtaining regression of electrocardiogram's alterations, serologic markers of cardiac damage and symptoms. Unfortunately, test for ADAMTS13 was not performed.

We immediately started steroid therapy at the dosage of 1 mg/kg/day and PE. PEs were performed for ten courses in which patient's plasma was replaced with virus-inactivated plasma. PE was stopped on day 41 because of a stable increase in platelets count ($87 \times 10^9/\text{L}$), a stability of hemoglobin level with no transfusions dependence, a normalization of bilirubine and lactate dehydrogenase (Fig. 1) and, finally, a complete disappearance of schistocytes in peripheral blood smear. Nevertheless, serum creatinine level remained at approximately 1.8 mg/dl . After 100 days post-transplant the reassessment of disease

Fig. 1 Trend of haemoglobin, LDH, total bilirubine, creatinine and platelets, from diagnosis to day 100

showed a partial response (IMWG criteria) with normal blood tests including hemoglobin and platelets values, but with a state of chronic renal failure.

Unfortunately, in June 2012, the patient experienced a relapse of MM with skin involvement and despite a salvage chemotherapy, his clinical condition rapidly worsening. He died after 2 months from relapse for disease progression: there was no evidence of TA-TMA relapsing during all this period.

Discussion

TA-TMA occurs when endothelial injury in the context of HSCT causes microangiopathic haemolytic anemia and

platelet consumption, resulting in thrombosis and fibrin deposition in microcirculation.

Idiopathic TTP, usually treated with PE, is caused by acquired or congenital decrease or deficiency of ADAM-TS13 [3], whereas pathophysiology of TA-TMA is not well understood and its identification can be very difficult. The incidence of TA-TMA has been reported with highly variable frequencies following both allogeneic (0.5–15 %) and autologous (0.1–0.25 %) SCT [4].

Immunosuppressive agents, like cyclosporine, may trigger the initiation of the disease in TA-TMA occurring after allogeneic SCT, while endothelial cell injury due to high-dose chemotherapy is more likely involved in post autologous TA-TMA. High-dose chemotherapy (intravenous Melphalan) and the previous CMV reactivation, even if negative at the time of cardiac symptoms onset, may be considered two possible trigger events in this patient.

At the present time, there is no consensus on appropriate therapy for patients with TA-TMA and it is not clear if PE is truly beneficial [5]. The prognosis of patients treated with PE is poor with high mortality rates. Jodele et al. [6] described a retrospective review of ten consecutive pediatric patients treated with PE for TA-TMA, indicating that patients receiving PE earlier in their disease course had a greater benefit than those starting later. Even if the role of PE in the management of TA-TMA is controversial, we observed an excellent response to PE, probably due to the early TA-TMA's diagnosis and the immediate start of PE treatment.

Although TA-TMA almost exclusively affects the kidney [7], some studies have identified the involvement of other organs, including the lungs and the gastrointestinal tract [8]. Furthermore, several case reports describe myocardial infarction with poor outcome in patient with idiopathic TTP [9]. However, symptomatic cardiac involvement in patients with TTP is infrequently reported despite autopsy studies demonstrating cardiac microthrombi [9] and there are no reports regarding cardiac involvement of TA-TMA [10]. The mechanism of action of PE, whether removal of inflammatory medications involving endothelial activation and microvascular thrombosis, remains to be investigated. Controlled studies on the use of PE in TA-TMA do not exist and results are

confounded by the incomplete understanding of its exact therapeutic mechanism. More research is needed to determine the pathogenesis of TA-TMA and to identify potential variables that may predict PE response.

Conflict of Interest The authors declare no financial or other potential conflicts of interest.

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