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THROMBOTIC THROMBOCYTOPENIC PURPURA: A RARE LATE COMPLICATION OF ALLOGENEIC BONE MARROW TRANSPLANTATION

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ABSTRACT

Thrombotic thrombocytopenic purpura/hemolytic uremic syndrome (TTP/HUS) usually occurs in a setting of systemic infection or graft-versus-host reaction during the first weeks following transplant. We report a case of fatal TTP that developed eight months after allogeneic bone marrow transplantation (BMT) without any evident association with other transplantation-related complications. Conditioning chemotherapy could have induced the disorder by causing damage to the vascular endothelium. The removal of immunosuppression, including cessation of cyclosporin A (CyA), may have precipitated the disease.

Key words: allogeneic BMT, thrombotic microangiopathy, thrombotic thrombocytopenic purpura, late complications, ANLL

Thrombotic thrombocytopenic purpura (TTP) is a systemic multi-organ syndrome characterized by thrombocytopenic, microangiopathic hemolytic anemia, fever and neurological symptoms. It is well established that TTP is a rare complication in allogeneic bone marrow transplantation. This syndrome is usually reported during the first phase of transplant, suggesting a relationship between TTP and other early complications of BMT, including cytomegalovirus (CMV) infection, graft versus-host disease (GVHD) or drug toxicity.[1-3] We report a case of TTP that developed eight months after BMT without any evident association with other transplantation-related complications, indicating that TTP might also be considered among the late complications of BMT.

Case Report

A 30-year-old female was admitted to our Hematology Department in June 1992 with fever and pancytopenia. Bone marrow smears showed leukemic cells morphologically consistent with acute non-lymphoid leukemia (ANLL), FAB subtype M5a. The diagnosis was confirmed by cytochemistry and surface markers. The patient achieved a complete remission after induction chemotherapy with cytosine arabinoside, VP-16 and idarubicin. Two months after intensification therapy with mitoxantrone and high-dose cytosine arabinoside she was referred for transplantation. Following conditioning therapy with cyclophosphamide (Cy) 120 mg/kg and busulphan 16 mg/kg, she received histocompatible sibling bone marrow in September 1992. Except for mild mucositis and alopecia, no other toxicity was observed following ANLL chemotherapy and the BMT conditioning regimen. The engraftment was adequate and the patient never developed signs of acute or chronic GVHD. Prophylaxis against GVHD consisted of cyclosporin A and short-term methotrexate

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(MTX) according to the Seattle scheme. The patient received routine oral anti-fungal agents and acyclovir. The early post-transplant period was complicated by CMV viremia on day +30, therefore ganciclovir (10 mg/Kg /day) was added to the treatment for fourteen days. The following post-transplant period was unremarkable. CyA was discontinued seven months after transplantation.

One month later, the patient developed fever, myalgias, dyspnea and petechiae. A blood count revealed thrombocytopenia (70×10^9/L). A bone marrow biopsy showed trilineage engraftment with bone marrow cellularity of 60% and an all-donor karyotype, thus confirming the complete remission status. Chest X-ray was negative, while echocardiography revealed pericardial effusion. Microbiological cultures were negative. Empirical antimicrobial treatment, corticosteroids and diuretics were started. A week later the patient experienced disturbance of vision, mental confusion and dysarthria without fever or hypertension. A CT scan of the brain was normal. There was no evidence of chronic GVHD or CMV infection, which was excluded by the absence of pp65-positive polymorphonuclear leukocytes and by the PCR technique. A blood count showed anemia (Hb 10.6 g/dL), thrombocytopenia (plt 20×10^9/L), while blood film examination revealed marked red cell fragmentation. Serum lactate dehydrogenase was 2,300 IU/L (normal range 220-450). Prothrombin time was moderately increased and Coombs' test was negative. Serum creatinine was 3 mg/dL. Urinanalysis revealed slight proteinuria (0.4 gr/L) and microhematuria. A diagnosis of TTP was formulated and daily 3-liter fresh frozen plasma-exchanges were begun immediately and continued for the following two weeks, together with prednisolone 80 mg/day and, on day +5, ticlopidine 500 mg/day. Though prompt significant neurological improvement ensued, there was a progressive deterioration in renal function so that hemodialysis had to be instituted 21 days after TTP diagnosis. Platelet count remained low (20×10^9/L) and serum lactate dehydrogenase elevated (2,000 U/L). Subsequently, various types of treatment were attempted: high-dose methylprednisone (500 mg/day × 4), vincristine (1 mg ×2 doses) and high-dose intravenous immunoglubulins (1.6 g/kg iv.). These therapeutic measures did not influence the downhill course of the disease, and the patient died of respiratory distress 58 days after admission without signs of ANLL recurrence. Permission for autopsy was not given.

Discussion

In the present case treatment-resistant TTP complicated by severe renal failure occurred eight months after allogeneic BMT for ANLL. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome (TTP/HUS) have been reported in at least 30 patients who underwent BMT.[1-5] Usually these complications occur during the first weeks following transplant, in a setting of systemic infection or graft-versus-host reaction. Although the etiology of post-BMT TTP/HUS is not clear, drug toxicity is probably a significant factor in cases with delayed onset of disease. Furthermore, it is interesting to note that as a late complication of BMT in the 5 cases reported so far[2,4,5] this syndrome often coincided with the withdrawal of CyA. TTP occurred in our patient without any evidence of other known etiological factors one month after the removal of CyA treatment. The fact that there was an apparent temporal relationship between CyA termination and the initiation of TTP suggests that discontinuation of immunosuppression plays a role in this syndrome. As proposed by Tschuchnigg et al., initial damage to the vascular endothelium brought about by conditioning chemotherapy could be the inciting event. In other words, endothelial damage might have mounted an immunologic response leading to the formation of anti-endothelial antibodies and immune complex deposition,[6] a process which might have been controlled by CyA and precipitated by its withdrawal. Similar etiological mechanisms may also apply to TTP developing as a complication of autologous[4,6] and syngeneic BMT.[8] Moreover, thrombotic microangiopathy has been described as a late complication (up to 20 months after treatment) of antineoplastic

therapy for malignant solid tumors[9] and hemopathies.[10]

In conclusion, although further research is necessary to identify those individuals who are at particular risk for TTP/HUS, we suggest evaluating the cytokine levels and the coagulation factors correlated with endothelial damage[7] before discontinuing immunosuppressive therapy.

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