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LETTER TO THE EDITORS

A case of thrombotic micro-angiopathy after heart transplantation successfully treated with eculizumab

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Dear Sirs,

The term thrombotic micro-angiopathy (TMA) defines a histological lesion of the arterioles and capillaries [1,2]. The clinical characteristics of this entity include microangiopathic hemolytic anemia, thrombocytopenia, and lesions in various organs. A considerable number of drugs such as immunosuppressants, chemotherapy drugs, and vascular endothelial growth factor inhibitors have been reported to cause dose-related or exposure time-related TMA. Calcineurin inhibitors can cause endothelial dysfunction in transplanted patients and increase platelet aggregation, inducing a TMA in some patients.

Here, we report a 42-year-old woman with advanced heart failure who underwent heart transplantation because of a restrictive cardiomyopathy. In the pretransplantation study, a mild anemia (hemoglobin 11.8 g/dl) and thrombocytopenia (platelets 118 000/ul) were found. Renal function was normal. The patient developed a cardiorenal syndrome type I refractory to medical treatment, requiring hemofiltration. Twenty-four hours later and based on the patient's poor clinical condition, an intra-aortic counterpulsation balloon was implanted, and an urgent heart transplantation was performed 7 days later. Induction therapy consisted of I.V. methylprednisolone bolus and basiliximab. Tacrolimus and mycophenolate mofetil were started 48 h after transplantation. Initial clinical course was satisfactory, but severe anemia (hemoglobin, 7.1 g/dl) and thrombocytopenia (46 000/mm^3), together with a marked increase of lactate dehydrogenase (LDH) (1097 IU/ml) were detected 7 days after transplantation. Coincidentally, the patient developed oliguria with renal function impairment (serum creatinine 1.5 mg/dl), and hemofiltration was started. A peripheral blood smear examination showed 2–3 schistocytes per field and a direct Coombs test was negative.

Due to the persistence and severity of the hematological abnormalities and the deteriorating renal function, a decision was made to withdrawn tacrolimus for its probably involvement in these complications. Peak levels of tacrolimus were 8 ng/ml. Despite tacrolimus discontinuation, anemia and thrombocytopenia worsened in the following days, together with an increase in LDH and persistence of schistocytes in blood smear. In addition, the patient began to present serious neurological complications, with delirium and convulsions, finally developing an status epilepticus. Autoimmunity studies were negative, except for low levels of the third complement fraction (70 mg/dl; normal values 83–171) and the fourth complement fraction (5.4 mg/dl; normal values 14–38). Serum levels of ADAMTS-13 were normal. The results of the study to identify potential gene mutations of the complement system or antibodies against its regulatory factors were negative. With the diagnosis of TMA, plasmapheresis sessions with infusion of fresh plasma were started. However, after the completion of five plasmapheresis sessions, analytical data of microangiopathic hemolytic anemia persisted, renal function had worsened, and the persistence of the status epilepticus seriously compromised the life of the patient. In this situation, it was decided to initiate treatment with eculizumab. Initial dose was 1200 mg, followed by 900 mg weekly (3 doses) and two more fortnightly doses of 1200 mg each (Fig. 1). Ten days after the onset of eculizumab, a progressive improvement of renal function, disappearance of hematological abnormalities, and complete recovery of neurological complications were observed. Heart graft showed a normal function and, to prevent a new exposure to tacrolimus, everolimus was added to the immunosuppressive therapy along with mycophenolate mofetil and steroids. Endomyocardial biopsies performed at months 1 and 3 after transplantation were normal. The patient was discharged three months after transplantation, showing an excellent clinical status with no sequela of her neurological complications. Renal function was normal (serum creatinine, 0.54 mg/dl; estimated glomerular filtration rate, 123 ml/min/1.73 m^2) as well as the hemogram (hemoglobin 12.1 g/dl, platelet count 210 000/ul), LDH (250 IU/ml) and serum haptoglobin (250 mg/dl).

Thrombotic micro-angiopathy is a rare but dangerous disorder in organ transplantation. The most common

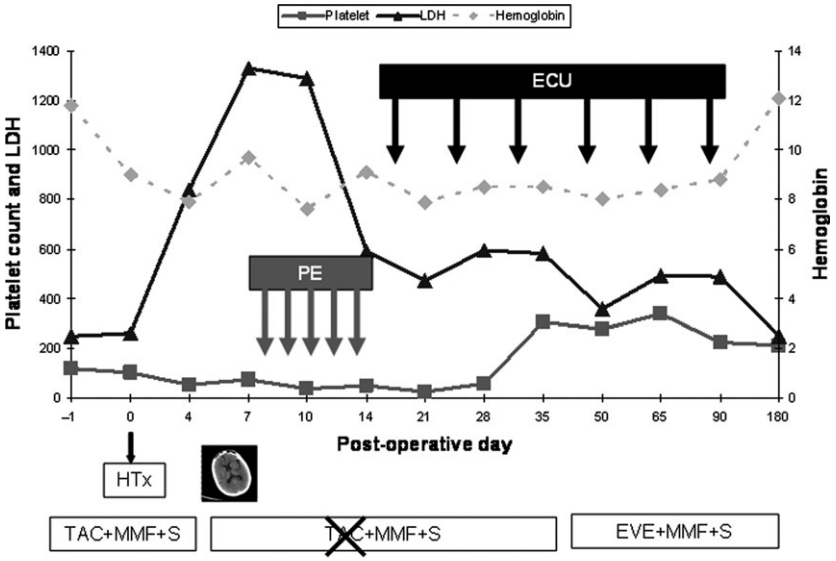

Figure 1 Evolution of hemoglobin, platelet count and LDH after transplantation.

causes of post-transplant TMA are anticalcineurin drugs, certain viral infections, and acute organ rejection [3]. Information about TMA developing after heart transplantation is scarce, although cases of TMA due to calcineurin inhibitors [4] and mammalian target of rapamycin (mTOR) inhibitors [5] have been reported. There are numerous pathways by which these immunosuppressant drugs can induce TMA, including an imbalance among vasoconstrictor and vasodilator mechanisms. It has been recently shown that exposure of endothelial cells to calcineurin inhibitors induces the release of a considerable number of microparticles into the circulation, which activates the alternative complement pathway [6].

Treatment of TMA secondary to drugs primarily consists of the discontinuation of the offending drug. Plasmapheresis has been used as an adjuvant measure for speeding the disappearance of TMA and associated complications. However, some patients are resistant to these measures. Recent studies have suggested that complement blockade by eculizumab can be effective not only in atypical hemolytic uremic syndrome but also in several other types of TMA [7,8].

Our patient is a clear example of how complement blockade by eculizumab can be life-saving in critical drug-induced TMA patients who did not respond to drug discontinuation and plasmapheresis. Eculizumab induced a rapid and dramatic resolution of neurological symptoms and a complete recovery of hematological and kidney dysfunctions. Other recent clinical reports have also illustrated the beneficial effects of eculizumab in patients with drug-induced TMA after transplantation [9] and in patients with TMA developing after heart transplantation [10]. In conclusion, eculizumab can be an effective therapeutic measure in cases of TMA secondary to tacrolimus with no response to drug withdrawal and plasmapheresis.

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