CLINICAL VIGNETTE

The Association of Thrombotic Microangiopathy with Hematopoietic Stem Cell Transplantation

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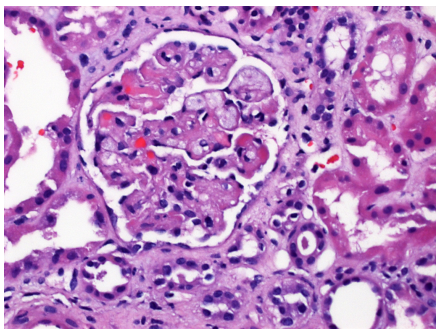
Case Report

A 49 year old male with history of acute lymphoblastic leukemia, who underwent an allogenic hematopoietic stem cell transplant after undergoing chemotherapy with hyper-CVAD (cyclophosphamide, vincristine, doxorubicin and dexamethasone) along with rituxan and imatinib followed by intrathecal methotrexate and cytarabine and total body radiation, was enrolled in a post transplant study to receive tacrolimus and sirolimus. He presented with acute kidney injury with creatinine steadily rising from 1mg/dL to 3mg/dL over 5 months after transplant. His hemoglobin also decreased from 10g/dL to 8g/dL.

On exam, vitals were temperature of 98.5 degrees F, blood pressure of 108/70 mm Hg, and pulse of 105. He was thin but in no acute distress. Although he was tachycardic, rhythm was regular. Mucous membranes were moist, lungs were clear, and there was no lower extremity edema present.

Laboratory studies were remarkable for hemoglobin of 7.3g/dL, platelets of 20,000, lactate dehydrogenase of 869 units/L, haptoglobin of less than 10, and peripheral smear with schistocytes. Spot urine protein to creatinine ratio was 4.85. Tacrolimus and sirolimus levels were 1.5 and 5.4 respectively. Serum creatinine was 3mg/dL. Renal ultrasound found 11cm kidneys bilaterally with no evidence of hydronephrosis. A renal biopsy was obtained and shown below.



The patient was diagnosed with renal thrombotic microangiopathy, which was attributed to tacrolimus and sirolimus. Both medications were slowly tapered over two months. Serum creatinine levels decreased to 2.6mg/dL and stabilized. He continued to get supportive care with packed red blood cell transfusions to maintain a hemoglobin level of 9g/dL and platelet transfusions to maintain a level of 40,000.

Discussion

Thrombotic microangiopathy is a common complication of hematopoietic stem cell transplantation. It is a pathologic process where endothelial cell injury leads to microangiopathic hemolytic anemia and platelet consumption. As a result, thrombosis occurs in the microcirculation, with kidney and brain most commonly affected. Renal histologic features include arteriolar and/or glomerular intracapillary thrombosis[1]. Cho, et. al. compared Blood and Marrow Transplant Clinical Trials in 2005 with the European Group Blood and Marrow Transplantation in 2007 to identify diagnostic criteria for thrombotic microangiopathy. Criteria for probable thrombotic microangiopathy included: at least 2 or more schistocytes per high power field, elevated lactate dehydrogenase levels, platelets less than 50,000 or a decrease in platelets by at least 50%, decrease in hemoglobin level, decrease in haptoglobin and negative Coombs test[2].

The mechanism of endothelial injury induced by tacrolimus includes direct cytotoxic damage, platelet aggregation, elevated von Willebrand factor, and decreased prostacyclin and nitric oxide production. Sirolimus prevents the repair of injured epithelium and decreases local vascular endothelial growth factor production, as shown in a study by Sartelet, et. al. Four cases of thrombotic microangiopathy in calcineurin inhibitor-free regimen of sirolimus alone in cadaveric kidney transplants were studied. Quantified expression of vascular endothelial growth

factor by immunostaining of renal biopsies identified weak expression in podocytes[2]. A retrospective cohort study done by Cutler et. al. looked at patients exposed to sirolimus with a calcineurin inhibitor versus calcineurin inhibitor therapy alone in the development of thrombotic microangiopathy in allogenic hematopoietic stem cell transplantation. 10.8% of the 111 patients exposed to sirolimus with calcineurin inhibitor therapy developed thrombotic microangiopathy compared to only 4.2% of 216 patients on calcineurin inhibitor therapy alone. This was statistically significant with a p value of 0.03[3].

Treatment options are limited and include discontinuation of the offending agent with possible therapeutic plasma exchange. A review article compared 11 studies where patients diagnosed with thrombotic microangiopathy after hematopoietic stem cell transplantation were treated with therapeutic plasma exchange. The median response was 36.5% with overall mortality of 80%; therefore, plasma exchange is currently not the standard of care[4]. The definitive treatment for these patients requires further study.

REFERENCES

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