CASE REPORT

Eculizumab in Transplant Associated Thrombotic Microangiopathy (Ta-Tma) at a centre in southern part of India

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ABSTRACT

Hematopoietic Stem Cell Transplantation (HSCT) is known to cause thrombotic microangiopathy with an incidence of 7%, but the diagnosis can be delayed due to cytopenias and organ toxicity. We present a case of 36-year-old male with chronic idiopathic neutropenia who developed TMA after a matched sibling donor PBSCT.

Key Words: *Hematopoietic stem cell transplantation; Thrombotic microangiopathy; Eculizumab*

INTRODUCTION

Hematopoietic Stem Cell Transplant (HSCT) has revolutionised the treatment of life-threatening diseases by prolonging patient survival and improving quality of life. It has a few complications and Thrombotic Microangiopathy (TMA) is one of them [1]. HSCT related factors lead to endothelial cell activation and complement dysregulation, leading to end organ dysfunction and even death. Transplant-associated Thrombotic Microangiopathy (TMA) leads to generalized endothelial dysfunction leading to multiorgan injury, and severe cases are associated with poor outcomes after Hematopoietic Stem Cell Transplantation (HSCT) [2]. Recent advances have implicated complement as a major contributor and the therapeutic potential of complement inhibition has been explored. Eculizumab has widely gained acceptance as a therapy for terminal complement blockade.

CASE PRESENTATION

We present a case of 36-year-old male who presented with aphthous ulcers, recurrent bouts of upper respiratory infection and neutropenia in 2019. He was treated with antibiotics and was found to have persistent neutropenia. Hematological evaluation was done and a diagnosis of chronic idiopathic neutropenia was made. A Matched Sibling Donor Peripheral Blood Stem Cell Transplant (MSD-PBSCT) was performed in August 2019. He was then started maintained on Prednisolone and MMF in the post-transplant period. His baseline creatinine at the time was 0.9 mg/dl. He recovered well. In Nov 2019, he developed acute Graft Vs Host Disease (GVHD) of the gut. His creatinine also gradually started increasing then to 2 mg/dl. He was presumed to have pre renal AKI at the time due to recurrent diarrheal episodes due to gut GVHD and was conservatively managed. In February 2020 he presented with pedal edema and hypertension and his creatinine was found to be 4.8 mg/dl. He was also found to have anemia, thrombocytopenia and raised LDH. Peripheral smear showed presence of schistocytes. He was diagnosed to have thrombotic microangiopathy and was initiated on Plasma Exchange (PLEX). He received 6 sessions of PLEX and 2 doses of Inj. Rituximab despite which his creatinine continued to rise. He was given a few sessions of hemodialysis as he remained refractory to treatment and his renal parameters worsened and he developed oliguria and volume overload. A renal biopsy was done in March 2021 which was suggestive of Thrombotic Microangiopathy. In April 2020, he was started on Inj.Eculizumab 300 mg IV once a week for a total of 9 doses. He responded well and creatinine started to decline serially. His LDH levels also declined. His steroid and MMF were gradually tapered off. Currently his creatinine is stable at 3.2 mg/dl and he is off dialysis. He is also hypertensive and is being managed on anti hypertensives.

HISTOPATHOLOGY FINDING

Light microscopy

Thirteen glomeruli, none are obsolescent. Stained with H & E, PAS,

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MT and PASM Glomeruli: The glomeruli show variable stages of thrombotic microangiopathy. Two glomeruli show expanded blood filled capillaries with mesangiolysis indicating early form of thrombotic microangiopathy. Upto eleven glomeruli appear lobular and show mesangiolysis with presence of fragmented RBC's in the mesangial region and endothelial swelling occluding the glomerular capillary lumen. In addition, three glomeruli reveal fibrin thrombi within the glomerular capillary lumen. One of them show partially oriented active cellular crescent formation. There is no necrotizing lesion. Tubules show moderate degree of acute tubular injury. Interstitium lacks inflammation. There are no granuloma or eosinophils. There is mild focus of tubular atrophy and interstitial fibrosis (10%-15%). There is mild intimal fibroplasia of the arteries. There is no necrotizing arteritis in the wall /or vasculitis.

Immunofluorescence

Twelve viable glomeruli are seen. Glomerular tufts show trapping of C3 (2+) in the tufts. Glomerular tufts are negative for granular deposits with a panel of antisera (IgG, IgA, IgM, C1q). Kappa and Lambda light chain stains do not show restriction. There are no extra-glomerular deposits [3].

Impression

Thrombotic microangiopathy (glomerular form), acute & subacute phase. Acute tubular injury (moderate degree) (Table 1).

TABLE 1
Lab investigations

Year	Aug-19	Feb-19	Mar-20	Apr-20	May-20	Jun-20	Jul-20	Aug-20	Aug-21
Creatinine (mg/dl)	0.9	4.8	5.4 - 6.2	6.2	5.4	4.16	4.5	2.98	3.2
Platelet Count (×10^3)	-	35	84	-	130	150	100	122	125
LDH	-	349 - 450	354	189	178	-	-	-	-

DISCUSSION & CONCLUSION

Transplant-Associated Thrombotic Microangiopathy (TA-TMA) is an increasingly recognized complication of Hematopoietic Stem Cell Transplant (HSCT) with increased morbidity and mortality. Histologic characteristics are the criterion for diagnosis of TA-TMA, although bleeding risk often prevents tissue examination. The disease ranges from self-limited illness to multi-organ dysfunction leading to death. The kidney is typically the primary site of microangiopathy, causing proteinuria, acute kidney injury, hypertension, development of chronic kidney disease, or end stage renal disease. TA-TMA has consistently been shown to have an adverse effect on non-relapse mortality and overall survival. Kidney involvement is a significant prognostic factor associated with poor survival and highlights the need for early recognition.

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