LETTER TO THE EDITOR

Mechanisms of endothelial injury and transplant-associated thrombotic microangiopathy in tandem autologous hematopoietic stem cell transplant for neuroblastoma

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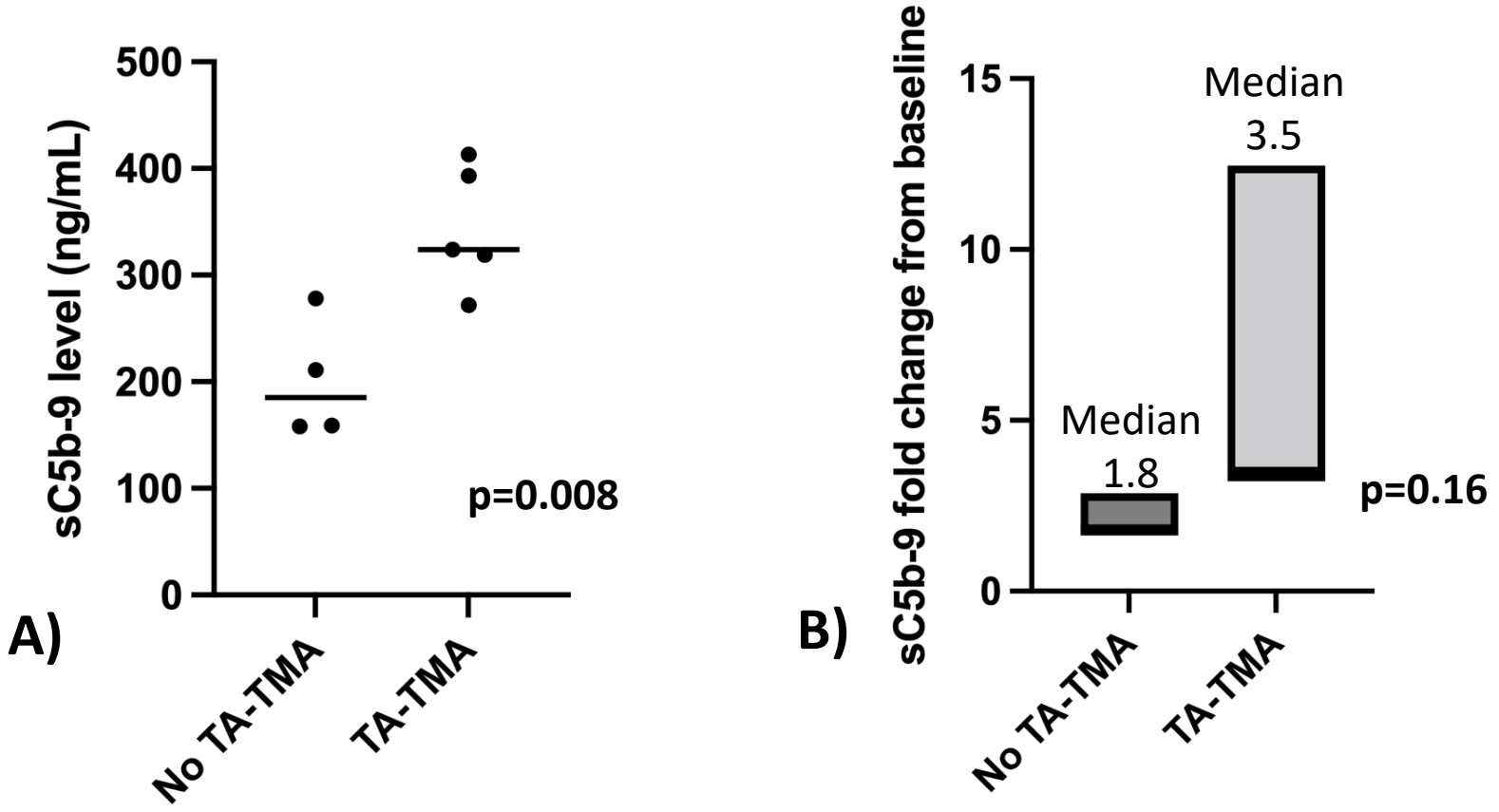
	Patient 1	Patient 2	Patient 3	Patient 4
Age at First Auto-HSCT	2 years old	2 years old	3 years old	2 years old
Sex	Female	Male	Male	Female
Diagnosis	Neuroblastoma	Neuroblastoma	Neuroblastoma	Neuroblastoma
Neuroblastoma Risk; INRGSS Stage	High; M	High; M	High; M	High; M
Pre-HSCT Curie Score	Auto-HSCT 1: 0 Auto-HSCT 2: N/A	Auto-HSCT 1: 1 Auto-HSCT 2: N/A	Auto-HSCT 1: 0 Auto-HSCT 2: N/A	Auto-HSCT 1: 6 Auto-HSCT 2: 2
Conditioning	Auto-HSCT 1: Cy/Thio Auto-HSCT 2: CEM	Auto-HSCT 1: Cy/Thio Auto-HSCT 2: CEM	Auto-HSCT 1: Cy/Thio Auto-HSCT 2: CEM	Auto-HSCT 1: Cy/Thio Auto-HSCT 2: CEM
Graft	Auto-HSCT 1: PBSC Auto-HSCT 2: PBSC	Auto-HSCT 1: PBSC Auto-HSCT 2: PBSC	Auto-HSCT 1: PBSC Auto-HSCT 2: PBSC	Auto-HSCT 1: PBSC Auto-HSCT 2: PBSC
TA-TMA Diagnosis	Yes	Yes	Yes	No
TA-TMA Diagnosis Day (days from auto-HSCT 1, auto HSCT 2)	77, 10	57, 6	65, 9	N/A
TA-TMA Risk Category	High	High	High	N/A
Eculizumab Therapy	Yes	No	Yes	No
Eculizumab Start Day (days from auto-HSCT 1, auto-HSCT 2)	77, 10	N/A	67, 11	N/A
Hepatic VOD	No	Yes	No	No
Defibrotide Therapy	No	Yes	No	No

Supplemental Table 1: Demographics and complications in Auto-HSCT recipients with CEC measurements (n=4). International Neuroblastoma Risk Group Staging System (INRGSS) was used for neuroblastoma staging. Transplant-associated thrombotic microangiopathy (TA-TMA) risk was based on Jodele criteria. Auto-HSCT= autologous hematopoietic stem cell transplant, CEM= carboplatin, etoposide and melphalan, Cy/Thio= cyclophosphamide and thiotepa, HSCT= hematopoietic cell transplant, PBSC= peripheral blood stem cells, M= metastatic, VOD= veno-occlusive disease, y/o= years old.

Supplemental Table 2: *In vitro* TA-TMA serum experiment patient demographics. Stored serum samples from patients transplanted between 2017 and 2022 were used. Jodele criteria were used for TA-TMA diagnosis and risk assignment. Steroid exposure was defined as methylprednisolone or stress dose hydrocortisone use between stem cell infusion and the time of sample collection. Serum from patients 1 and 3 in the CEC kinetics experiments were also included in the TA-TMA cohort of this study. CEM= carboplatin, etoposide, melphalan, Cy/Thio= cyclophosphamide and thiotepa, auto-HSCT= autologous hematopoietic stem cell transplant, IQR= interquartile range, TA-TMA= transplant-associated thrombotic microangiopathy.

	TA-TMA Patients (n=5) % (n) or median (IQR)	**No TA-TMA Patients (n=4)** % (n) or median (IQR)
Age (years)	4.1 (2.9-7)	3.7 (2.4-4.6)
Sex		
Male	80% (n=4)	25% (n=1)
Diagnosis		
Neuroblastoma	100% (n=5)	100% (n=4)
Preparative regimen		
Auto-HSCT 1: Cy/Thio, Auto-HSCT 2: CEM	100% (n=5)	100% (n=4)
Day of TA-TMA diagnosis	9 (4-10)	N/A
TA-TMA risk group		
High	100% (n=4)	N/A
Received eculizumab		
Yes	100% (n=5)	0% (n=0)
Eculizumab start day	10 (7.5-14)	N/A
Serum sample collection day	7 (5.5-10.5)	7 (7-7.75)
Received steroids		
Yes	80% (n=4)	75% (n=3)
Methylprednisolone	60% (n=3)	25% (n=1)
Stress dose hydrocortisone	20% (n=1)	50% (n=2)



Supplemental Figure 1: Soluble C5b-9 levels in patient blood used for *in vitro* culture experiments. A) sC5b9 levels in patients with TA-TMA obtained prior to eculizumab initiation and compared to timepoint matched controls without TA-TMA. Levels were measured in thawed specimens to ensure terminal complement did not degrade during frozen storage time. **B)** sC5b-9 levels from figure A were compared to the baseline sC5b-9 levels obtained clinically for each patient, the fold increase is shown for TA-TMA patients and control patients without TA-TMA. The solid black horizontal line in each figures A and B indicates the median. Statistical analyses were performed using two tailed T-test. TA-TMA= transplant-associated thrombotic microangiopathy.