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Severe, persistent neurotoxicity after transplant-associated thrombotic microangiopathy in a pediatric patient despite treatment with eculizumab

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Abstract

Background: TA-TMA is a described complication of aHCT in children with neuro-blastoma. Outcomes are poor with mortality rates approaching 60%. Described late effects in survivors include chronic kidney disease and persistent pulmonary hypertension.

Case: We report a case of a 2-year-old with neuroblastoma who developed severe TA-TMA 35 days after high dose chemotherapy and autologous stem cell rescue. He presented with respiratory failure, pericardial and pleural effusions, hemolysis, hy-pertension, and mild altered mental status. He was mechanically ventilated for 3 weeks and after sedation was lifted, he was minimally responsive. He was treated with eculizumab with resolution of hemolysis, kidney injury and polyserositis. Initially he was more responsive; however, after almost a year of intensive therapy he re-mained nonverbal and had persistent irritability and behavioral changes. He had an extensive negative evaluation. On day +345, he presented with severe, refractory epilepsy. Three years after TA-TMA, he continues to have severe neurologic disabilities.

Conclusions: To our knowledge, persistent neurologic toxicity has not been reported in TA-TMA. However, deficits and seizures are reported in other TMAs, particularly in children with atypical HUS who present with significant neurologic changes at di-agnosis. Our patient's persistent neurologic disability despite eculizumab response in all other involved organs may reflect irreversible damage. This case describes a new long-term sequela of TA-TMA and highlights the need for further studies to under-stand both acute and long-term neurologic complications of this disease.

Keywords

autologous transplant; eculizumab; epilepsy; neuroblastoma; neurotoxicity; TA-TMA

1 | BACKGROUND

TA-TMA is a complication of HCT that can range from a mild self-limited illness to multisystem organ failure and death. Severe TA-TMA with multiorgan failure occurring

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after aHCT for neuroblastoma is well described, and conditioning with CEM is an identified risk factor.^{1,2} The pathophysiology of TA-TMA after aHCT is thought to be multifactorial involving dysregulation of the complement alternative pathway in the setting of endothelial damage from chemotherapy, infection, or immune dysregulation.^{3,4} There are many proposed diagnostic criteria for TA-TMA, though schistocytes, anemia, and thrombocytopenia are common in the four major criteria: blood and marrow clinical trials network toxicity committee,⁵ international working group,⁶ probable TA-TMA,⁷ and refined TA-TMA criteria from Jodele et al.³

Most of the current literature focuses on the acute impact of TA-TMA. However, persistent renal dysfunction is described including chronic kidney disease and hypertension. In a retrospective study of adults, patients with TA-TMA had 4.3 times the risk of developing chronic kidney disease.⁸ In one report in children, kidney function decreased by 65% after TA-TMA.⁹ Other long-term complications have not been reported other than one pediatric patient with chronic pulmonary hypertension that required 11 months of treatment with sildenafil but ultimately resolved.¹⁰

Historically, therapy for TMA was supportive care. Recently, eculizumab, a complement blocking agent, has been used as targeted therapy for TA-TMA with improvement in outcomes.^{11–13} In a pediatric cohort with high-risk TA-TMA, defined as proteinuria >30 mg/dL and evidence of complement system activation (elevated s5b-9) 1-year overall survival after treatment with eculizumab was 56% compared to 9% for untreated patients ($P = 0.003$).¹⁴ In addition to improving overall survival, improvement and resolution of acute neurologic toxicities after eculizumab therapy is repeatedly reported.^{15,16} For optimal effect in TA-TMA, eculizumab is dosed weekly for 4 weeks, and thereafter dosed to maintain a CH50 level of 0–3 CAE for an additional two weeks, and then stopped.¹³

2 | CASE PRESENTATION

A 2-year-old boy presented with a rapidly growing axillary mass and was ultimately diagnosed with stage 4 high-risk neuroblastoma. He was treated as per Children's Oncology Group protocol ANBL12P1 with five cycles of induction chemotherapy, surgical resection, and subsequent MIBG therapy for persistent MIBG-avid disease. Prior to proceeding to high-dose chemotherapy with CEM with autologous stem-cell rescue, he had good organ function and a normal neurologic examination. Though he did not have a formal neurocognitive assessment, developmentally he was thought to be appropriate by his providers and family. He was able to speak in full sentences, build towers of blocks, do puzzles on his tablet computer, walk unassisted, and had a Lansky play-performance score of 100%.

The child developed increased work of breathing necessitating transfer to the ICU for respiratory support that evolved to multiorgan dysfunction by day +5 after HCT. He had elevated LDH, anemia and thrombocytopenia requiring frequent transfusion support, acute kidney injury (serum creatinine of 2.6 mg/dL corresponding to an estimated GFR of less than 15 mL/min/1.73 m²), proteinuria (225.1 mg/dL), a negative Coombs test, normal coagulation studies, schistocytes on peripheral blood smear, an ADAMTS13 activity assay

of 44% (reference range for adults 70%, <10% highly indicative of ADAMTS13 deficiency and TTP), and an elevated CH50 level of 183 CAE units (reference range >145 high). Thus, he met criteria for TA-TMA at day +35 by all four accepted diagnostic criteria.^{3,5–7} Additionally, the child had characteristic clinical manifestations of severe TA-TMA; he was hypertensive, was intubated for 3 weeks with bilateral pleural effusions which required chest tubes, and had a pericardial effusion with tamponade physiology, requiring pericardiocentesis. He did not have evidence of pulmonary hypertension or gastrointestinal symptoms.

In terms of his neurologic course, shortly after HCT cell infusion, his family thought he was more sleepy than usual and “not quite right,” which was attributed to his severe acute illness. He was then intubated and sedated from day +5 to day +29. Per institutional ICU standard of care, he had reactive pupils and was noted to have spontaneous movement, but no detailed assessment of neurologic function was performed. After extubation on day +29, he was minimally responsive and did not interact with his caregivers. A head CT obtained that day demonstrated moderate volume loss thought to be related to therapy. Brain MRI on day +33 showed stable known skull lesions and moderate volume loss. Initially, a posterior pituitary bright spot was appreciated in the setting of hypernatremia consistent with diabetes insipidus. On multiple repeat MRIs, this was decreased and of unclear clinical significance. There were never diagnostic parenchymal signal abnormalities. EEG was negative for seizures. Lumbar puncture was performed with CSF cell counts within normal limits and infectious studies negative. All findings, including the altered mental status, were attributed to TA-TMA, and he was treated with eculizumab 600 mg on day +35. Eculizumab was dosed to maintain a CH50 level of less than three CAE after a 4-week induction course (Figure 1).

Within 4 weeks of treatment with eculizumab, his hematologic parameters normalized and the hypertension and polyserositis resolved. Treatment was stopped after 6 weeks with no laboratory evidence of TMA (nine total doses). After his first dose of eculizumab, he became more alert with small improvements in his ability to pay attention. However, he continued to have waxing and waning mental status and remained nonverbal, non-ambulatory, and NGT-dependent for feeds. He was enrolled in physical therapy, occupational therapy, and speech therapy. He regained the ability to walk around day 240, but his other deficits persisted. He had multiple MRIs of his brain that were normal. There were no clinical concerns about seizure activity, though no further EEGs were performed. His developmental regression was thought to be multifactorial including post-traumatic stress from his very severe illness.

Almost one year after HCT (day +345), the patient presented to the clinic to start his sixth cycle of neuroblastoma-directed antibody therapy, and his family reported he was now falling more than 20 times a day and had new-onset difficulty walking. He had a head CT that was normal and unchanged from previous images. EEG demonstrated 67 seizures with clinical correlation, consistent with epileptic spasms. Brain MRI showed no evidence of intracranial metastatic disease or structural changes/lesions to explain his new seizures. He had a lumbar puncture with negative infectious studies, normal oligoclonal bands, IgG, neopterin, and a negative paraneoplastic panel (Table 1).

He was initiated on Keppra and ultimately was refractory to four additional seizure medications and cannabis oil. He continues to have 20–30 drop seizures a day and around 1–2 tonic-clonic seizures a week. His most recent EEG demonstrated bursts of paroxysmal fast activity in the setting of multifocal spikes, consistent with LGS. Additional workup for the seizure disorder included multiple brain MRIs which remain normal outside of his stable residual disease of his skull bones and a normal metabolic workup. His neurologists attribute his refractory seizure disorder to sequelae of his TA-TMA.

At 5 years of age, he continues to have an unstable gait and poor head control, requires the use of a helmet for his frequent drop seizures, and is unable to ambulate. He is completely NGT-dependent for nutrition. He has about 10 words that he rarely uses though he occasionally communicates with gestures and follows simple commands. He knows his name and recognizes his parents, though not his sibling. His surveillance scans continue to demonstrate stable residual MIBG-avid disease, and the family has opted for no additional cancer-directed therapy at this time.

3 | DISCUSSION

Neurologic manifestations of TA-TMA are reported in up to 30% of patients; however, the underlying pathophysiology of CNS complications is not well understood.^{3,17,18} Described CNS clinical manifestations at TA-TMA presentation include PRES, confusion, drowsiness, headaches, hallucinations, and seizures. There are no characteristic imaging findings in patients with CNS involvement, and imaging findings consistent with PRES are present in only a minority of patients.¹⁹ To our knowledge, there are no reports of persistent neurologic deficits in survivors of TA-TMA. However, there are reports of long-term CNS and cognitive deficits in other TMAs, aHUS, and TTP.

aHUS is more common in children than TTP, and thus, there are more data on associated neurologic changes. In a large retrospective study of 90 children with aHUS that occurred during an out-break of *Escherichia coli* 0104:H4, 26% of patients presented with neurologic complications, primarily seizures, and altered mental status. After treatment with eculizumab and/or plasmapheresis, 18/23 (78%) patients had resolution of neurologic changes. One child had persistent major deficits (dyskinesia after cerebral edema), and three had moderate persistent deficits. At the time of reported follow-up (4 months), all children were improving.²⁰ In a cohort of 52 children with aHUS who had severe neurologic involvement at presentation, neurologic sequela occurred more frequently.²¹ These children presented with seizures, stuporous coma, pyramidal syndrome, hemiplegia/hemiparesia, and/or extrapyramidal syndrome. Twelve of the 52 (25%) had severe, persistent disabilities. Five had mild sequelae, 26 had full neurologic recovery, and nine died. Most patients had abnormal MRI findings including parenchymal ischemia and hemorrhagic lesions, but three had no MRI changes despite the dramatic neurologic presentation of severe coma or clinical pyramidal syndrome.²¹

TTP, a rare and often fatal disorder if untreated, can have a more waxing and waning course, making identifying long-term neurologic changes more challenging. However, persistent neurologic injury after TTP in remission has also been reported in 27 adult patients as

evidenced by an abnormal MRI (39%) and neurocognitive impairment in tests of visual learning and memory (63%).²²

Because of his respiratory failure, our patient was intubated and sedated at the time of his TA-TMA presentation and we are thus unable to comment on his neurologic status for nearly 3 weeks beyond knowing that he had spontaneous movement. It is possible that he had severe deficits at presentation that were not appreciated until his extubation on day +29. If so, perhaps as reported in aHUS, severity at presentation increased his risk of persistent disabilities, despite resolution of all other organ involvement following eculizumab therapy.

Our patient had evidence of hemolysis, acute renal injury, and hypertension on day +5 after stem-cell infusion. However, he was not diagnosed with TA-TMA until day +35, the first day he was noted to have schistocytes in his peripheral blood smear. At that point, additional testing including CH50 was sent and supported the diagnosis. It is now thought that in cases of severe TA-TMA, schistocytes may be absent or delayed due to high vascular permeability and red blood cell extravasation into the tissues.²³ While he was treated with eculizumab as recommended and had therapeutic CH50 levels, it is unknown if treating him earlier in his disease course would have altered his outcome.

LGS is a form of severe epilepsy that is characterized by refractory seizures with a characteristic EEG pattern and intellectual disability.²⁰ Developmental delay and associated behavioral problems are common and sometimes progressive decline occurs in the setting of poorly controlled seizures. LGS is known to occur in the setting of CNS damage or trauma. Thus, neurologists attribute this patient's initial developmental delay and subsequent development of LGS to a late effect from TA-TMA.

In conclusion, we describe a child who developed severe TA-TMA and, despite response of all other involved organs after treatment with eculizumab, had significant and progressive neurologic deficits. This case highlights the need for careful monitoring of mental status changes in children diagnosed with TA-TMA, so the incidence of both acute and long-term neurologic complications can be understood. The role of early treatment with eculizumab can then be evaluated in terms of impacting ultimate neurologic recovery.

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Abbreviations:

aHCT	autologous hematopoietic cell transplantation
aHUS	atypical hemolytic syndrome
CAE	complement activity enzyme
CEM	carboplatin/etoposide/melphalan
CNS	central nervous

CSF	cerebrospinal fluid
CT	computed tomography
EEG	electroencephalogram
ICU	intensive care unit
LDH	lactate dehydrogenase
LGS	Lennox-Gastaut syn-drome
MIBG	metaiodobenzylguanidine
MRI	magnetic resonance imaging
NGT	nasogastric tube
PRES	posterior encephalopathy
TA-TMA	transplant-associated thrombotic microan-giopathy
TTP	thrombotic thrombocytopenic purpura

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FIGURE 1.

Clinical course of patient from day 0, when stem cells infused to day 100. The figure depicts laboratory data consistent with TA-TMA including transfusion-dependent anemia and thrombocytopenia, and elevated creatinine and LDH. Clinically, he developed respiratory failure requiring intubation, hypertension requiring two medications for control, and polyserositis requiring a pericardial drain and chest tube. He was treated with eculizumab (E) and had an appropriate response with CH50 levels between one and three CAE units after two doses

TABLE 1

Workup for new seizure disorder

Study	Result	Reference range
CSF		
Total protein	15.2 mg/dL	15–45 mg/dL
Glucose	55 mg/dL	60–80 mg/dL
WBC	2/mm ³	0–7
RBC	2/mm ³	0–50
Lymphocyte	95%	
Monocyte	5%	
Albumin	11 mg/dL	0–35 mg/dL
Albumin Index	2.8	0–9
IgG	1 mg/dL	0–6 mg/dL
Oligo bands IgG	732 mg/dL	423–1090 mg/dL
Oligo Bands IgG Index	0.49	0.28–0.66
IgG/albumin ratio	0.09	0.09–0.25
IgG synthesis rate	<0.0 mg/d	8.0
Oligo bands	Negative	Negative
Oligo bands number	0	0–1
Neopterin	18 nmol/L	7–65 nmol/L
Gram stain and culture	Negative	Negative
Oligo bands albumin serum	3970 mg/dL	3500–5200 mg/dL
Autoimmune encephalopathy (CSF)		
NMDA-R antibody	Negative	Negative
VGKC-complex Ab IPA	0.00 nmol/L	0–0.02 nmol/L
GAD66 Ab assay	0.00 nmol/L	0.02 nmol/L
GABA-B-R Ab CBA	Negative	Negative
AMPA-R Ab CBA	Negative	Negative at <1:2 titer
Anti-neuronal nuclear Ab, type 1	Negative	Negative at <1:2 titer
Anti-neuronal nuclear Ab, type 2	Negative	Negative at <1:2 titer
Anti-neuronal nuclear Ab, type 3	Negative	Negative at <1:2 titer
Anti-glial nuclear Ab, type 1	Negative	Negative at <1:2 titer
Purkinje cell cytoplasmic Ab, type 1	Negative	Negative at <1:2 titer
Purkinje cell cytoplasmic Ab, type 2	Negative	Negative at <1:2 titer
Purkinje cell cytoplasmic Ab, type Tr	Negative	Negative at <1:2 titer
Antiphysin Ab	Negative	Negative at <1:2 titer
CRMP-5-IgG	Negative	<1:2 titer
Vitamin B12 level	1962 pg/mL	190–778 pg/mL
Methylmalonic acid	0.6 mcmmol/L	0–0.8 mcmmol/L
Serum acylcarnitine	Normal pattern	
Plasma amino acids	Normal pattern	