

Review

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Transplant-Associated Thrombotic Microangiopathy (TA-TMA) in Childhood - A literature review

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Introduction

Transplant-associated thrombotic microangiopathy (TA-TMA) refers to inflammatory and thrombotic diseases [1]. The definition of TA-TMA includes microangiopathic hemolytic anemia, intra vascular activation of platelets, and finally thrombus formation of platelets; white clot within the micro - circulation. TA-TMA is a well-recognized complication of HSCT. This syndrome occurs in 10% to 20% of the patients with allogenic hematopoietic stem cell transplants (HSCTs). It is much less frequent in the autologous setting [1]. TA-TMA occurs in different organs including the kidneys, gut, lungs, liver and also brain. Multiorgan failure is observed in the majority of patients affected with TA-TMA [2]. The median time to TA-TMA onset is approximately 30-45 days after HSCT [2].

Transplant-associated thrombotic microangiopathy (TA-TMA) is considered one of the most severe complications after hematopoietic stem cell transplantation (HSCT). Transplant-associated thrombotic microangiopathy (TA-TMA) constitutes a form of microangiopathic haemolytic anemia and thrombocytopenia derived from a generalized endothelial dysfunction with intravascular platelet activation and formation of platelet-rich thrombi within the microcirculation. Since clinical features are common in several post hematopoietic stem cell transplantation (HSCT) complications such as capillary leak syndrome, engraftment syndrome, graft versus host disease (GVHD), diffuse alveolar hemorrhage and veno occlusive disease (VOD), an initial diagnosis of TA-TMA is not always certain, which is a principal reason for the failure of proposed treatments.

Keywords: Thrombotic Microangiopathies; Hematopoietic Stem Cell Transplantation; Child; Hemolytic-Uremic Syndrome; Eculizumab.

Running Title: Transplant-Associated Thrombotic Microangiopathy

The disease ranges from a mild, self-limited form to an uncontrolled fulminant disease leading to death. The mortality rate is approximately 30-80% [2]. JODELE et al reported that 1-year NRM was 43.6% ± 8% in subjects with TMA and 7.8% ± 3.8% in HSCT subjects without TMA (P, .0001) [3]. TA-TMAs present diagnostic challenges because they may not clearly fall into one of the categories of the 2 major TMAs: atypical hemolytic uremic syndrome (aHUS) and thrombotic thrombocytopenic purpura (TTP) [1]. In addition, complications that might occur during transplantation are in the differential diagnoses of TA-TMA. These events include infections, graft-versus-host disease (GVHD), disseminated intravascular coagulation (DIC), and side effects of some immunosuppressive drugs [1].

Therefore, an initial diagnosis of TA-TMA is not always certain, which is a principal reason for the failure of proposed treatments in the past.

Pathogenesis in TA-TMA

The pathogenesis of transplant-associated TMA is not very clear. It is believed that the disease starts with endothelial damage. The abnormalities in vascular endothelium are independent of ADAMTS13 deficiency. TMA is a pathological definition and characterized by fibrinoid necrosis in vessel walls and arteriolar thrombus. Following intravascular thrombocyte activation due to endothelial damage, platelet thrombi develop in the microcirculation. This process depletes thrombocytes. RBC is mechanically damaged due to microcirculation obstructed by fibrin particles or small sized thrombi. Finally, the presentation would be microangiopathic hemolytic anemia & thrombocytopenia (Fig 1,2,3) [1,2,4-7].

Risk factors in TA-TMA (Fig 1,2) [4,5]

Most important risk factors for developing TA-TMA in the HSCT setting are as following:

- **Infections:** Aspergillus , CMV, adenovirus, Parvovirus B19, Human herpes virus-6, BK virus, (Viremia >10 000 copies/mL)
- **Calcineurin & Mammalian target of rapamycin inhibitors (Sirolimus).** They are able to damage endothelium directly and also activate the alternative complement pathway in an individual with a genetically based inability to control that system
- **GVHD , ‘cytokine storm’** (IL-8, IL-12, and thrombomodulin)
- **Activation of coagulation factors in Coagulation pathways and Endothelial factors**
- **Complement, Elevated levels of sC5b-9**
- **Female gender**
- **Age:** less frequent in children compared to adults
- **The extent of HLA mismatch**
- **Use of ATG**
- **Stem cell source:** (BM vs. PB)

Clinical signs in TA-TMAs [5]

- Anemia, thrombocytopenia -no immune mediated hemolysis or DIC. Hematuria
- Fever
- Mental disability
- Possible kidney Failure

Updated proposal of TA-TMA diagnostic parameter

Careful monitoring of clinical and laboratory TA-TMA markers for at least 3 to 5 consecutive days

from the onset of the disease should permit a better evaluation of other concomitant and confounding events, such as infections, engraftment syndrome, drug toxicities and other causes of cytopenia (decrease of Hb level and platelet count). The prognosis of the patients with TA-TMA is probably related to rapid diagnosis duo to preventing a spiralling cascade of systemic endothelial damage [1, 2].

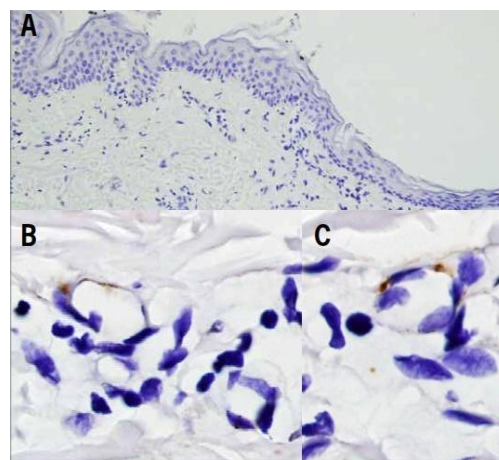


Fig 2. C5b-9 (MAC, membrane attack complex) deposition was detectable along the small vessels of the superficial dermis in B & C [1]

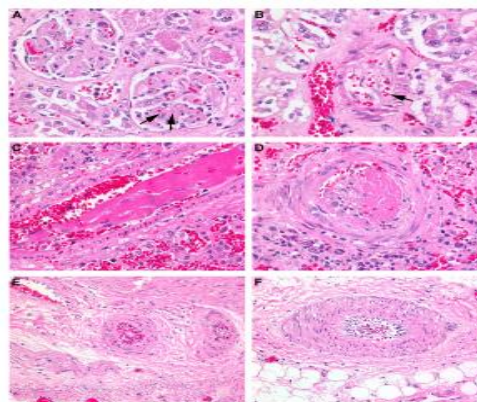


Fig 3: Histologic examples of TA-TMA affecting various organs. (A) Renal cortex with glomeruli, (B) Renal arteriole (C) Lung, (D) Pulmonary arteriole with a recent thrombus and extravasated red blood cells. (E-F) Mesenteric arterioles in the small bowel [4]

Classification of patients with TA-TMA includes “standard risk” and “high risk” based on the following criteria [2]:

Standard risk groups:

- Hb: unexplained/rapid decreased value

- Platelets: unexplained/rapid decreased value
- LDH: above upper limit of normal range compared to normal institutional values
- Schistocytes: more than 1- 2% per high-power field on 2 or more consecutive peripheral blood smears (PBS)
- Coombs test: negative
- TA-TMA Index (ratio between LDH/platelets:1000): = or >20

High Risk groups:

- Proteinuria: over 30 mg/dL
- Unexplained Hypertension resistant to two or more drugs therapy
- Serum sC5b-9: above normal range (i.e. 72-244 ng/mL)

Jodele et al in their single centre prospective study showed that in the early period after HSCT, evaluation of proteinuria, also a spot urine protein-to-creatinine ratio, could offer diagnostic and prognostic information for those patients likely to develop TA-TMA. They reported that proteinuria, elevated LDH levels and Hypertension were earlier markers (Fig 4).

They also reported that elevated serum C5b-9 levels with proteinuria were associated with very poor survival (<20% at 1 year). Evaluation of Complement and complement regulatory protein mutation analysis could be useful, but they did not recommend them as routine practice because they are expensive and the results may take weeks. They stated that available commercial platforms failed to identify known mutations in classic aHUS at least 30% of the time (Fig 5) [3].

Creatinine is a poor marker of kidney function for patients, due to the influence of the muscle mass, so creatinine would remain normal until significant renal dysfunction occurs. Kidney function, determined by nuclear glomerular filtration rate (GFR) is as the “gold standard,” test. Cystatin C, a recently introduced non-muscle-based marker of the kidney function is evaluated by a single blood test. It has proved to be a useful indicator of GFR. However, validating prospective data after HSCT is unavailable [4]. TA-TMA is a pathologic diagnosis. Renal biopsy is helpful to diagnose TA-TMA, especially in patients with clinical uncertainty. Renal biopsy is associated with a significant risk in patients post HSCT, because bleeding complications are common. However, kidney biopsy, if safe to do, provides useful prognostic and treatment information. Despite the high prevalence of renal diseases after HSCT, 2% of the patients undergo a renal biopsy [4]. Diagnosis of TA-TMA is complex, and at least three distinct sets of

criteria have been published (Table 1).

Parameter	Leukemia Net International Working Group	Blood and Marrow Transplant Clinical Trials Network	Overall Thrombotic Microangiopathy (O-TMA) Grouping
Schistocytes	>4%	>2 per high-power field	>2 per high-power field
Platelet count	<50,000/mm ³ or <50% of normal baseline	NS	<50,000/mm ³ or <50% of normal baseline
Lactate dehydrogenase	Increased	Increased	Increased
Haptoglobin	Decreased	NS	Decreased
Transfusions	Increased	NS	NS
Creatinine	NS	2 × baseline	NS
Direct Coombs test	NS	Negative	Negative
Coagulation studies	Normal	Normal	Normal

Table 1. Definition of Thrombotic Microangiopathy Occurring in Hematopoietic Stem Cell Transplants: Comparison of 3 Different Sets of Criteria [1]

Treatment in TA-TMA [1-4].

There is no consensus on the therapy of TMA. Outcome is better when treatment is initiated within 7 days from the diagnosis. Treatments include:

- Doses of immunosuppressive drugs should be decreased or stopped
- Manipulation of GVHD prophylaxis
- Plasma Exchange (PE)
- Rituximab
- Defibrotide
- Evaluation for infections should be done
- Modulator endothelial cell inflammatory responses, such as statins & Antioxidant agents
- Eculizumab (Soliris, Alexion, Anti-C5)

Plasma Exchange (PE): PE has been a standard, effective treatment for TTP since 1991. PE has also been widely used for any form of TMA, including TA-TMA, for decades. A vast majority of the patients with TA-TMA have ADAMTS13 activity levels above 5%-10%; therefore, they should not be expected to respond significantly to plasma exchange unless an ADAMTS13-deficient state with activity of less than 5%-10% is present, instances of which appear to be quite rare. The risks of complications including infections due to plasmapheresis, catheter or

transfused plasma thrombosis and hemorrhage should be considered [1,4].

Rituximab (Anti-CD20): The exact mechanism of the action of rituximab in TA-TMA is not known. It has possible effects on controlling the immune function, production of antibody, or activation of complements. Like plasma exchange, rituximab is of limited or no clinical value in the majority TA-TMA patients with activity levels of ADAMTS13 more than 5% to 10% [1,4].

Defibrotide (Polydisperse Oligonucleotide): Defibrotide has antithrombotic and thrombolytic activities and anti-inflammatory and anti-ischemic effects. It inhibits TNF mediated endothelial cells. The main effect of defibrotide is local on the vascular bed [5].

Eculizumab (Soliris, Alexion, Anti-C5- Terminal Complement Inhibitor):

Eculizumab is a humanized monoclonal antibody. It has been available only since Sep 2011. Eculizumab is a therapeutic option for the severe HSCT complications with high mortality in patients with TA-TMA [8]. Jodele and colleagues reported 6 pediatric patients in whom TA-TMA with acute renal failure developed in the allo-HSCT setting. The majority of the patients had deletions of complement factor H-related proteins (CFHRs) [1 & 3].

3/6 patients also had auto AB to CFHR. Most had thrombosis on biopsy. The patients had poor responses to plasma exchange and elevated circulating MAC levels.

Children with HSCT-TMA required higher doses or more frequent eculizumab infusions. Eculizumab therapeutic level was >99 µg/mL. CH50 level ≤4 correlated with therapeutic eculizumab levels. HSCT-TMA resolved over time in 4 /6 children after achieving therapeutic eculizumab levels [9]. (Fig 5)

Administration Route of Eculizumab

Eculizumab is diluted to a final concentration of 5 mg/mL with 0.45% or 0.9% NS, 5% DW, or Ringer’s solution. It is administered intravenously over 35 minutes.

The duration may be slowed to 2 hours for patients who experience adverse effects. Supplemental doses of eculizumab should be administered within 60 minutes after each plasmapheresis or plasma exchange.

A supplemental dose should also be administered 60 minutes prior to each unit of fresh frozen plasma infused.

Use of Eculizumab in Younger Patients, According to Body Weight:

- **30 - 40 kg**, the induction phase consists of 600 mg given weekly for 2 doses, followed by 900 mg at week 3 and then every 2 weeks afterwards.
- **20-30 kg:** 600 mg weekly for 2 doses followed by 600 mg at week 3 and then every 2 weeks.
- **10-20 kg:** 600 mg at week 1, 300 mg at week 2, and then 300 mg every 2 weeks.
- **Infants between 5-10 kg** should receive 300 mg at weeks 1 - 2, then 300 mg every 3 weeks.

Warnings and Precautions, Eculizumab–Soliris

Black box warning has been added to the prescribing information for eculizumab to call attention to reports of life-threatening and fatal meningococcal infections in patients receiving treatment. The decrease in MAC formation produced by eculizumab eliminates one of the body’s defense functions against of *N. meningitides*. In normal situations, MAC binds to cell walls of the bacteria, resulting in increased permeability and cell death.

Therefore, patients should be immunized with meningococcal vaccine at least 2 weeks prior to administering eculizumab unless the risks of delaying therapy outweigh the risk of a meningococcal infection. Meningococcal vaccines are protective only against A, C, Y, and W-135 strains. Meningococcal vaccines are not protective against serogroup B.

The peak incidence of serogroup B strain is observed in children less than 5 years old and adolescents between 15 and 19 years of age. Therefore, the use of penicillin for prophylaxis is recommended in children receiving eculizumab to provide additional protection [8].

Adverse Effects of Eculizumab in TA-TMA [8]

The most common adverse effects reported by the 37 adults and adolescents receiving eculizumab in the two prospective aHUS studies were:

- Hypertension (in 35% of patients)
- Headache (30%)
- Anemia (24%)
- Leukopenia (16%)
- Diarrhea (32%)
- Vomiting (22%), Nausea (19%)
- Abdominal pain (11%)
- Infection in the urinary tract system and upper part of the respiratory system (35% and 16%)
- Insomnia (14%)
- Cough or sore throat (14%)

- Edema, fever, vertigo, musculoskeletal pain (11%).

Poor Prognostic Criteria in Patients with TA-TMA [5]

- Age equal to or greater than 18 years.
- Unrelated or haploidentical donor
- TA-TMA index (TA-TMAI), increased LDH/platelet ratio >20
- Schistocyte count > 5-10 HPF
- Patients not exposed to Sirolimus
- Presence of nephropathy

Conclusions

There are numerous identified causative agents for TA-TMA. Complement activation, either as the primary mode of injury or a secondary insult along a final common pathway of endothelial injury, suggests more prospective researches in the diagnosis and management of TA-TMA.

Conflict of Interest

None declared

Financial Support

None declared

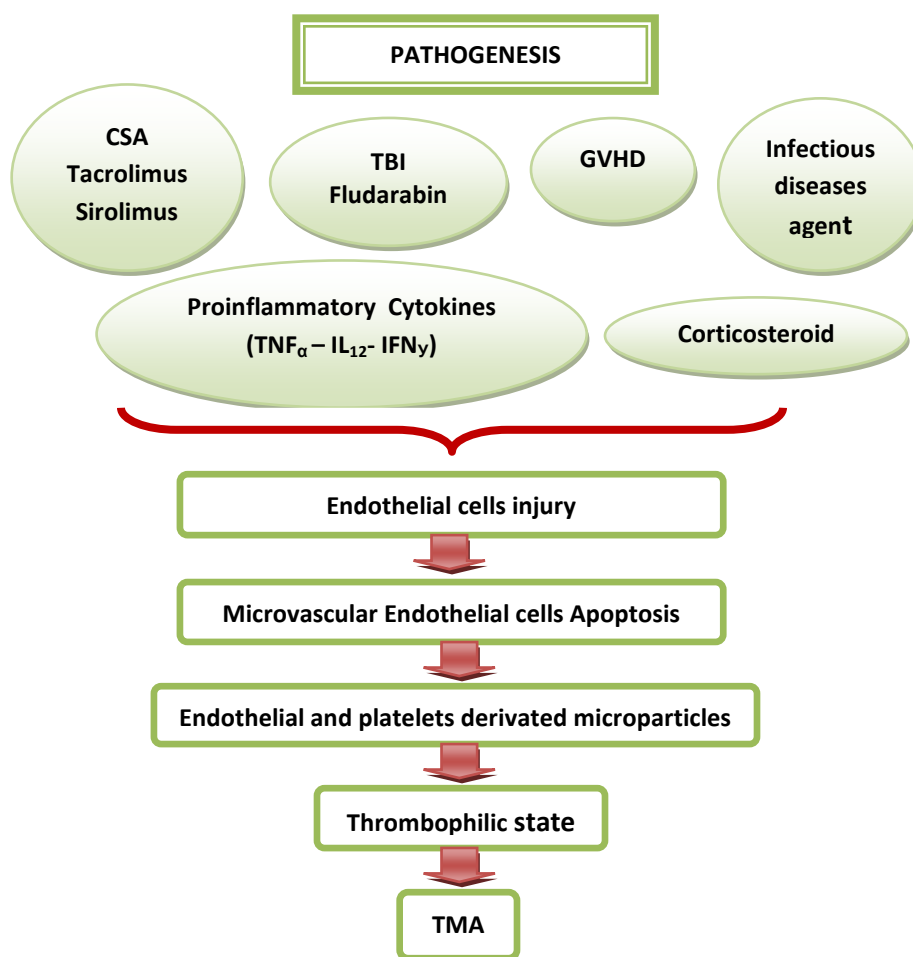


Fig 1. Pathogenesis of TA- TMA [5].

TA- TMA: Transplant-associated thrombotic microangiopathy, CSA: Cyclosporine, GVHD: Graft versus host disease, TBI: Total body Irradiation, TNF α : Tumor necrosis factor alpha, IL12: Interleukin12, IFN γ : Interferon gamma, TMA: Thrombotic microangiopathy

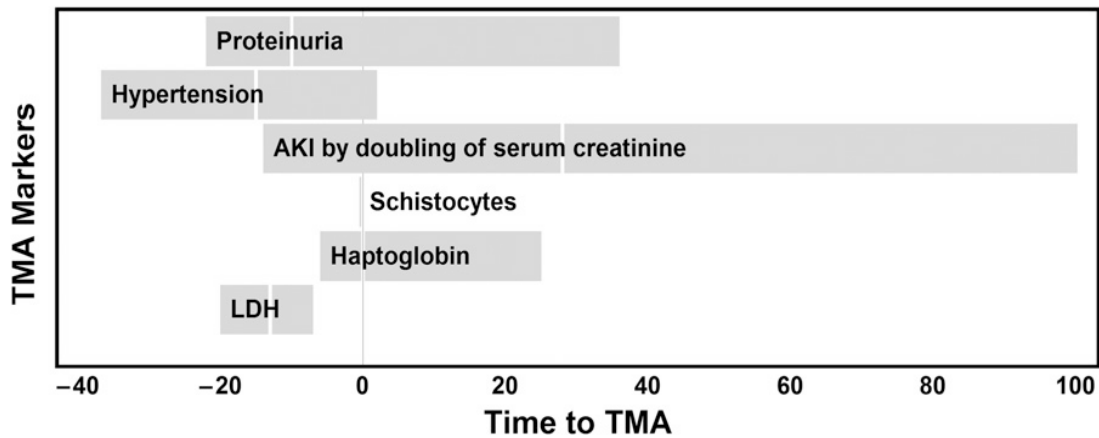


Fig 4. Time course of clinical and laboratory markers in relation to date of TMA diagnosis systolic hypertension, an elevated LDH, and proteinuria: 10 to 14 days prior to TMA diagnosis. A decreased haptoglobin lagged the first elevation in LDH by almost 2 weeks AKI (acute kidney injury) defined as doubling of the serum creatinine, almost a month after TMA diagnosis [3].

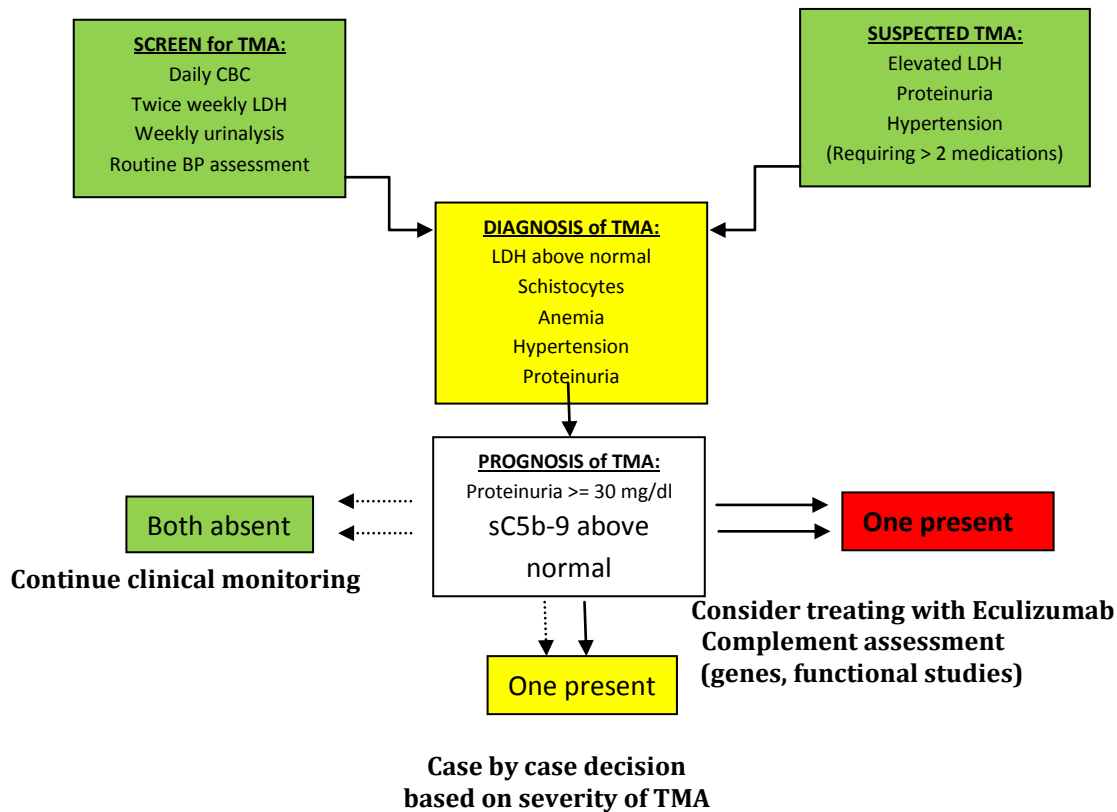


Fig 5. Algorithm for the evaluation of TMA after HSCT (3)

TMA: Thrombotic microangiopathy, **CBC:** Cell blood count, **LDH:** Lactic dehydrogenase, **BP:** blood pressure.

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