Transplant-Associated Thrombotic Microangiopathy (TA-TMA) in Childhood

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Thrombotic Microangiopathy (TMA) syndromes

Diversity

- Hereditary or acquired.
- They occur in children and adults.
- The onset can be sudden or gradual

Unity

- Clinical features
  - microangiopathic hemolytic anemia, thrombocytopenia, and organ injury
- Pathological features:
  - vascular damage that is manifested by arteriolar and capillary thrombosis with characteristic abnormalities in the endothelium and vessel wall
Pathology TMA

- TMA is a pathological definition and characterized by *fibrinoid necrosis in vessel walls and arteriolar thrombus*.

- Following intravascular *thrombocyte activation* due to microscopic damage, thrombus rich in thrombocytes develops in microcirculation.

- This process *depletes thrombocytes*.

- RBC are mechanically damaged due to microcirculation obstructed by fibrin particles or microthrombus.

- The clinical picture is *microangiopathic hemolytic anemia* and thrombocytopenia.
Pathological Features of the Nine Primary Thrombotic Microangiopathy Syndromes

(ADAMTS13 deficiency-mediated TMA)
Drug-mediated TMA (immune reaction)

- **Mechanism:**
  - non-dose-related idiosyncratic, immunologic reactions

- **Cause:**
  - Quinine: the only documented drug-dependent antibodies against multiple cells
  - Quetiapine and gemcitabine: recurrent acute episodes with repeated exposures

- **Clinical presentation:**
  - Initial presentation is a sudden onset—few hours—of severe systemic symptoms with anuric acute kidney injury
  - may be a history of illness after previous exposures
  - tablets or quinine-containing beverages
  - negative drug-dependent antibodies test does not exclude a drug association.

- **Treatment:**
  - Removal of drug, supportive care
  - Plasma exchange is often begun because TTP is suspected and a drug-mediated cause is uncertain.

- **Outcome:**
  - Chronic kidney disease with hypertension is common.
  - End-stage renal disease may occur.
Drug-mediated TMA (toxic dose–related reaction)

**Mechanism:** dose- and timedependent toxicity
- Calcineurin inhibitors (such as cyclosporine and tacrolimus) and immunosuppressive, chemotherapeutic agents: induce direct endothelial dysfunction and increased platelet aggregation, possibly through the inhibition of prostacyclin.
- Vascular endothelial growth factor-VEGF- inhibition: impair function in renal endothelial cells and podocytes causes gradual development of glomerular TMA
- Multiple potential mechanisms (e.g., immunosuppressive, chemotherapeutic agents,

**Clinical presentation:**
- Gradual onset of renal failure occurs over weeks or months.
- Abrupt, severe TMA may occur, as with intravenous abuse of the opiate oxymorphone

**Treatment:**
- Removal of drug, supportive care
- For some drugs, such as calcineurin inhibitors, dose reduction, rather than drug avoidance, may be sufficient

**Long-Term Outcomes**
- Microangiopathic hemolytic anemia and thrombocytopenia often resolve.
- Renal failure may persist.
Algorithm for the Evaluation of Children and Adults Presenting with TMA

Microangiopathic hemolytic anemia with thrombocytopenia

Underlying disorders (common in adults, uncommon in children)

Kidney injury

Sudden onset (systemic symptoms, anuria within hours)
- Drug (immune, uncommon in children)
- ST-HUS (Shiga toxin, more common in children)
- Acquired complement (more common in children) and hereditary complement (probably equally common in children)

Acute onset (several days of illness preceding kidney injury)
- Coagulation (probably more common in children)
- Metabolism (probably more common in children)

Long-term onset (weeks or months of progressive kidney injury)
- Drug (toxic, uncommon in children)
- Acquired TTP (uncommon in children) and hereditary TTP (more common in children)

No or minimal kidney injury
Definition Transplant-Associated Thrombotic Microangiopathy (TA-TMA)

- TMA
- Multi factorial mechanisms:
  - Ability to damage endothelium directly
  - Activate the alternative complement pathway in an individual with a genetically based inability to control that system.
- Multiorgan: typically manifests as renal impairment, pulmonary hypertension, polyserositis, gastrointestinal symptoms, CNS injury
- 11,000 Autologous and 7000 allogeneic: in USA
  - 10% - 20% of patients with Allogeneic HSCT
  - Much less frequent in the Autologous setting
- TA-TMAs, occur a median of 150 days (mean 90 days) after transplant
  - Range: mild, self-limited form to uncontrolled fulminant disease leading to death
Risk factors for TA-TMA

- HSCT conditioning regimens: busulfan, fludarabine, platinum-based chemotherapy,

- Infections: Aspergillus, CMV, adenovirus, Parvovirus B19, human herpes virus-6, BK virus, (Viremia >10,000 copies/mL)

- Calcineurin and mammalian target of Rapamycin inhibitors (sirolimus): ability to damage endothelium directly, to activate the alternative complement pathway in an individual with a genetically based inability to control that system

- GVHD: TA-TMA were 4 times higher in patients with acute GVHD

- Cytokines: Elevated levels of circulating cytokines, including IL-8, IL-12, and thrombomodulin, during TA-TMA

- Coagulation cascade and endothelial markers
Risk factors for TA-TMA

- Female gender
- Age: less frequent in children compared to adults.
- The extent of HLA mismatch is one factor.
- Severity of the primary disease
- Use of ATG
- Total body irradiation
- Stem cell source (BMA, PB)
Clinical signs TA-TMAs

- Occur a median of 150 days (mean 90 days) after transplant
- In 2/3 of the cases, the disease occurs before 100 days
- RBC fragmented by microangiopathic damage and erythrocyte turnover increases without immune mediated hemolysis or DIC.
- PS: fragmented RBC (schistocytes).
- Mild hemolysis, severe Anemia, thrombocytopenia
- Fever
- Hematuria
- Mental disability
- Kidney failure requiring dialysis may be present in patients.
Biochemically

- LDH is increased
- Haptoglobin level is decreased
- Indirect hyperbilirubinemia and hemoglobinuria
- Fragmented erythrocyte ratio is 4-10% in transplant-associated TMA.
- NRBC in peripheral circulation
- Thrombocyte consumption is increased although DIC is not present.
- Plasma vWF level is high albeit not pathognomonic
  - vWF level increases more in allogeneic stem cell recipients compared to Autologus recipients.
  - The highest levels of vWF are seen in 3-4 months after the transplantation when TMA is also clinically presented.
Diagnostic Markers in TA-TMA in 100 children and young adults undergoing HSCT
(Sonata Jodel et al.)

- ADAMTS13 activity: greater than 5% in 39/100 of children and young adults undergoing HSCT who had TAM
- Elevated LDH levels, hypertension, and proteinuria on routine urinalysis: earliest markers of a TMA
- Elevated serum C5b-9 levels with proteinuria were associated with very poor survival (<20% at 1 year).
- Complement and complement regulatory protein mutation analyses could be useful, but they do not recommend as routine use.
  - Tests: expensive, results may take weeks, and available commercial platforms fail to identify known mutations in Classic aHUS at least 30% of the time.
Time course of clinical and laboratory markers in relation to date of TMA diagnosis

- Proteinuria
- Hypertension
- AKI by doubling of serum creatinine
- Schistocytes
- Haptoglobin
- LDH
Definition of Thrombotic Microangiopathy Occurring in Hematopoietic Stem Cell Transplants: Comparison of 3 Different Sets of Criteria

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LeukemiaNet International Working Group(^{36})</th>
<th>Blood and Marrow Transplant Clinical Trials Network(^{28})</th>
<th>Overall Thrombotic Microangiopathy (O-TMA) Grouping(^{34})</th>
</tr>
</thead>
<tbody>
<tr>
<td>Schistocytes</td>
<td>&gt;4%</td>
<td>&gt;2 per high-power field</td>
<td>&gt;2 per high-power field</td>
</tr>
<tr>
<td>Platelet count</td>
<td>&lt;50,000/mm(^3) or &lt;50% of normal baseline</td>
<td>NS</td>
<td>&lt;50,000/mm(^3) or &lt;50% of normal baseline</td>
</tr>
<tr>
<td>Lactate dehydrogenase</td>
<td>Increased</td>
<td>Increased</td>
<td>Increased</td>
</tr>
<tr>
<td>Haptoglobin</td>
<td>Decreased</td>
<td>NS</td>
<td>Decreased</td>
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<tr>
<td>Transfusions</td>
<td>Increased</td>
<td>NS</td>
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<tr>
<td>Creatinine</td>
<td>NS</td>
<td>2 × baseline</td>
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<td>Direct Coombs test</td>
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</tr>
<tr>
<td>Coagulation studies</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
</tr>
</tbody>
</table>

NS, not specified.
Diagnostic criteria for transplant-associated TMA

- Presence of schistocytes
- Presence of prolonged or progressive thrombocytopenia (<50x10^9/l) or 50% or more decrease in the previous thrombocyte count
- Sudden and persistent LDH increase
- Decrease in hemoglobin concentration or increase in transfusion needs
- Decrease in serum haptoglobin level

Each criteria needs to be fulfilled for diagnosis. Sensitivity and specificity are 80%
Kidney Biopsy / TA-TMA

- Renal biopsy can aid in the diagnosis of TA-TMA, especially in the presence of clinical uncertainty or significant renal dysfunction.

- This procedure carries significant risk in the post HSCT population in whom bleeding complications are common.

- Despite the high prevalence of renal disease after HSCT, 2% of patients underwent a renal biopsy.

- Kidney biopsy, when safe to perform, often provides useful prognostic and treatment information.
Treatment of TA-TMA

- Difficult to diagnose- Difficult to treat
  - There is no any consensus on the therapy of TMA.
- Decrease or stop immunosuppressive therapy
- Plasma Exchange :
  - PE has also been widely used for any form of TMA, including TA-TMA, for decades (since 1991)
  - TA-TMA therefore should not be expected to respond significantly to plasma exchange unless an ADAMTS13-deficient state with activity of less than 5% to 10% is present, instances of which appear to be quite rare.
  - Complications of TPE: infection, thrombosis, hemorrhage, pneumothorax, tamponade, serum sickness, allergy, hypotension
Treatment, TA-TMA

- **Rituximab**, is of limited or no clinical value in the vast majority of patients with TA-TMA, who have ADAMTS13 activity levels >5% to 10%.
- **Defibrotide** approve -Europe, Antithrombotic and thrombolytic activity, inhibits TNF mediated endothelial cell apoptosis, anti-inflammatory and anti-ischemic effects, Main effect is local on vascular bed.
- **Anti-CD25 antibody** (Daclizumab)
- **TNFα inhibitors** such as Etanercept and Infliximab
- A work-up for infections should be instituted
Eculizumab Therapy in Children with Severe Hematopoietic Stem Cell transplantation–Associated Thrombotic Microangiopathy.

*SONATA JODELE. 2014. Biology of blood and marrow transplantation*

- described 6 pediatric patients in whom TA-TMA with acute renal failure developed in the allogeneic HSCT setting.
- Dysregulation of the complement system may be involved in the pathogenesis of (HSCT-TMA):
  - C4d and C5b–9 deposition in tissues, has been demonstrated in the renal arterioles and other organs
  - Complement mutations have also been reported in TA-TMA
  - Deletions of complement factor H–related proteins (CFHRs) 1 and 3
    - 3 /6 also had autoantibodies to CFHR.
- The patients had poor responses to plasma exchange
- 4 /6 achieved therapeutic plasma levels of eculizumab and clinical responses to the drug
Treatment, TA-TMA
Eculizumab (Soliris, Alexion, Anti-C5)

- Available only since Sep 2011
- MAB - Anti C5 - inhibits C5a and C5b, thus preventing terminal complex C5-9, and hemolysis:
  - PNH
  - TMA
- Therapeutic level >99 μg/mL.
- Half life: 8-15 days
- Half life following TPE: 1.26 H
- CH50 level ≤ 4 complement activity enzyme units correlated with therapeutic eculizumab levels
Eculizumab (Soliris, Alexion, Anti-C5)

- 300 mg vials, 10 mg/mL
- Refrigerated until use
- Diluted to a final concentration of 5 mg/mL with 0.45% or 0.9% NS, 5% DW, or Ringer’s injection.
- IV infusion over 35 minutes,
- 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.
Ecluzumab Dosage

- 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.

- Upon discontinuation, patients should be monitored for at least **12 weeks** to identify any return of symptoms.
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%)
- Upper respiratory or urinary tract infections (35% and 16%),
- Insomnia (14%)
- Cough or throat pain (14%)
- Edema, Fever, Vertigo, Musculoskeletal pain (11%).
Algorithm for the evaluation of TMA after HSCT.
prognostic factors TA-TMA

- TA-TMA: Mortality rate of more than 60%
  - Age equal to or greater than 18
  - Unrelated or haploidentic donor
  - Increased TMA index (LDH/platelet ratio)
  - Schistocyte count > 5-10 hpf
  - Patients not exposed to sirolimus
  - Presence of nephropathy
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