THROMBOTIC THROMBOCYTOPENIC PURPURA

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Blood Matters
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Disclosure

- I have no potential conflicts of interest to disclose
Objectives

- Review epidemiology, presentation and pathophysiology of TTP
- Review treatment modalities and evidence
- Congenital and pregnancy-associated TTP
- Future directions
TTP

- Rare life-threatening thrombotic microangiopathies
- Medical emergency
- Shares some characteristics with atypical HUS
- Originally thought to be same disease
- Pathophysiology and treatment differ
Acquired TTP - Epidemiology

- 3 cases per 1 million adults per year

- Median age of diagnosis: 41
  - Range 9-78yo

- Rare in children <18yo
  - 1 per 10 million per year

- 75% cases female
TTP

- TTP results from deficiency of ADAMTS13
  - ADAMTS13 = disintegrin and serine metalloproteinase
  - Usually severe deficiency, activity <10%

- ADAMTS13 required for cleaving von Willebrand factor

- Acquired TTP: due to anti-ADAMTS13 autoantibodies

- Hereditary TTP: inherited ADAMTS13 mutation
TTP

- Widespread microthrombi that are platelet- and VWF-rich

- Classically diagnosed by pentad of findings:
  - Microangiopathic hemolytic anemia
  - Thrombocytopenia (plt <50 x 10^9/L)
  - Neurologic disturbances
  - Fever
  - Renal dysfunction

- 10% require intubation upon presentation
- Mortality 10-20%
TTP

• Causes:
  • Allogeneic HSCT
  • Pregnancy/Postpartum
  • Drug-associated
    • Quinine
    • Chemotherapy
    • Calcineurin inhibitors
  • Autoimmune conditions
  • Infections
  • Malignancies
  • Malignant HTN
TTP

http://imagebank.hematology.org/AssetDetail.aspx?AssetID=1344&AssetType=Asset
Role of ADAMTS13 measurement

- Controversial

- Lack of reproducibility between assays using VWF multimers or collagen binding
  - Indirect measure of ADAMTS13

- Identify very low ADAMTS13 levels

- Fluorescence resonance energy transfer (FRETS) assay now methodology of choice at many institutions

- Other assay methods:
  - Mass spectrometry
  - Enzyme-linked immunosorbent assay
TTP Treatment

• Hematologic emergency
  • Without treatment, progressive neurologic deterioration, cardiac ischemia, irreversible renal failure and death
  • Prior to 1980s, mortality rate 90%

• Patients should not be left overnight without plasma exchange
  • Referral to apheresis unit
  • Central venous line access
  • While awaiting plasma exchange:
    • plasma infusion and steroids

• Plasma exchange most important
  • Replaces large volume of plasma with ADAMTS13
  • Removes ADAMTS13 IgG antibody
  • High dose steroids should be considered

• With current treatments, >80% of patients recover
TTP Treatment

• Plasma exchange (PLEX):
  • Extracorporeal treatment that separates blood components (plasma and/or cellular components) from patient’s blood
  • Removal of patient’s plasma and replacement with another fluid
  • Used for conditions with pathogenic substance in blood causing morbidity

• Challenges of PLEX:
  • When to initiate
  • ADAMTS13 activity and inhibitor testing:
    • Often not immediately available
    • Not sufficiently sensitive or specific to use in isolation

• Risks
  • Citrate induced hypocalcemia
  • Metabolic alkalosis
  • Complications related to vascular catheter
  • Blood produce replacement = risk of transfusion reactions/transfusion transmitted diseases
  • Coagulation factor depletion
TTP - Treatment Approach

- Initiate PLEX as soon as possible upon presumptive dx
  - Can use Plasma infusion as temporizing measure
  - Do not wait for results of ADAMTS13 activity or antibody testing

- Oklahoma recommendations:
  - Give glucocorticoids to all patients
  - Rituximab may be appropriate for some patients immediately, but not typically as part of initial treatment
  - Supportive transfusions if bleeding or invasive procedures

- Continue PLEX until platelet count is normal for 2 days
  - (>150 x 10⁹/L)

- If diagnosis of TTP likely, but platelets remain low, or new neuro abnormality = refractory disease
TTP – Evidence for PLEX

• 1966 – Series of 255 patients
  • 75% died within 3 months
  • Many survivors were subsequently diagnosed with another condition or infection

• Two landmark clinical trials established efficacy of PLEX
  • 1991 – 102 TTP patients randomly assigned to PLEX or plasma infusion x 7 days
    • Survival PLEX vs plasma groups:
      • At 9 days: 96% vs 84%
      • At 6 months: 78 vs 63%
    • Response rates (based on platelet count) also higher in PLEX group
TTP – Evidence for PLEX cont’d

• Second landmark trial – 1991
  • 108 TTP patients
    • If minimal symptoms – treated with glucocorticoids alone (prednisone 200mg daily)
      • If no improvement after 48h, PLEX begun
    • If Moderate to severe symptoms - received PLEX plus glucocorticoids
      • 50% of patients fell into this group
  
  • Half received plasma infusion or glucocorticoids alone (prednisolone 200mg daily) initially
    • 44% had no response and were then treated with PLEX + steroids

• **91% survival rate**
• 64% relapsed overall
• High rate of failure amongst plasma infusion alone, so this treatment modality discontinued
TTP – PLEX

- Cryo-Poor Plasma and Pathogen-inactivated plasma equivalent to FFP
  - Small randomized trials and retrospective series found no difference in outcomes between PLEX using these agents vs. FFP

- Cryo-Poor plasma – lower content of VWF multimers
  - Thought might reduce formation of platelet-rich thrombi
  - Lower content of FVIII and fibrinogen
  - If used, must monitor coagulation assays and fibrinogen levels and alternate with another plasma product

- One estimated plasma volume (40ml/kg) daily until recovery
TTP - Glucocorticoids

- Use along with PLEX
- Lack of randomized trials, but observational studies support
- Thought to reduce ADAMTS13 inhibitor production
- Reduces number of PLEX exchanges required
- Also reduces cytokine production

- Milder symptoms: oral prednisone 1mg/kg per day
- Severe TTP: Methylprednisolone IV 125mg BID to QID

- Increase dose of steroids if plt count low after 3-4 days
TTP Treatment

- If initial disease severe or symptom progression → intensification of PLEX
  - i.e. twice daily or increase plasma volume (1.0 → 1.5)

- Upon clinical improvement → continue daily

- No indication to taper PLEX, as long as close surveillance
  - Monitor CBC, smear, LDH, Cr daily

- To improve response:
  - HAART in HIV associated TTP
  - Consider further immunosuppressive therapy, i.e. Rituximab
TTP treatment - Rituximab

- **Adjuvant therapy – Rituximab**
  - Small series and larger cohorts showed benefit in relapsing and refractory TTP

- 2011 Phase II non-randomized trial demonstrated benefit of Rituximab in acute TTP
  - Reduction in number of PLEX required to achieve remission
  - Reduction in inpatient days
  - Reduction in relapse rates

- Dose: Rituximab 375mg/m², administered weekly or q3-4 days

- Response takes median of 10 days

- **American recommendations--use Rituximab for:**
  - Severe disease
  - Major neurologic symptoms
  - Platelet count still low after 3-4 days
  - TTP exacerbation when PLEX discontinued
TTP treatment

- Relapses after rituximab = median 24 months
  - Confirmed in a 2012 French multicentre trial in relapsed/refractory acute TTP

- Pre-rituximab more frequent relapses

- Oklahoma Registry: 34% relapse rate
  - 60 TTP cases between 1989 and 2008

- Previously documented relapse rates: 30-50%
Monitoring after TTP

- Most treatment is associated with:
  - reduction in anti-ADAMTS13 IgG levels
  - Increase in ADAMTS13 activity

- Risk of relapse associated with:
  - Low ADAMTS13 activity – surrogate marker
    - may drop months before relapse
  - Presence of antibody

- Per BJH, British practice is to monitor ADAMTS13 activity levels during remission
  - A reduction in enzyme <10% is a marker to consider rituximab
  - Goal to normalize ADAMTS13 and prevent acute episode
  - May use lower dose Ritux (100mg/m²) electively

- In practice, we use:
  - CBC, LDH, smear, creatinine, neurologic symptoms
TTP

- 5% attain remission but ADAMTS13 activity remains low
- Requires vigilant monitoring of blood counts
- Rituximab and mycophenolate can be used
- Typically Afro-Caribbean patients
  - Pathophysiology unclear
- Cyclosporine effective
  - Side effects can be prohibitive
Recovery

- Median time to remission: 7-10 daily PLEX exchanges
  - Neuro symptoms and LDH usually improve first (~1 day)
  - Platelet count typically rises after 2-3 days

- 15-20% of patients have exacerbation once PLEX stopped
  - Keep CVC in place 5-7 days after stopping PLEX

- 20-25% relapse after remission, usually within first several years
Future directions

• Antibodies to von Willebrand factor:
  • Attempts to prevent VWF binding to platelets, thus preventing platelet microthrombi
  • TITAN trial (abstract) suggests may improve outcomes
    • Caplacizumab is antibody to vWF under review
    • Suggests faster platelet normalization in conjunction with PLEX
    • Increased remission rate

• Recombinant ADAMTS13:
  • Under study in clinical trials for patients with hereditary TTP
  • Uncertain whether application to patients with acquired TTP
Congenital TTP

- Upshaw-Schulman syndrome = congenital TTP

- Rare

- Require frequent monitoring to ensure plt >150 x 10^9/L
  - Maintain normal plt count to prevent end organ damage

- Achieve normalization with:
  - Plasma infusions
  - Factor VIII concentrate (contains measurable ADAMTS13)

- Pregnant women require regular plasma infusion to optimize outcome for mother and baby
Pregnancy associated TTP

- ADAMTS13 analysis required to differentiate congenital vs. acquired TTP

- Challenge of diagnosis
  - Spectrum of pre-eclampsia, HELLP, TTP
  - Shared signs/symptoms

- Should institute PLEX for Plt <50 x 10^9/L + MAHA
  - Or if other clinical signs suggest TTP
  - Mortality 90% without PLEX

- Women who have had TTP have a higher risk of pregnancy-related complications

- Commonly occurs postpartum, not ameliorated by delivery
Questions & References


