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

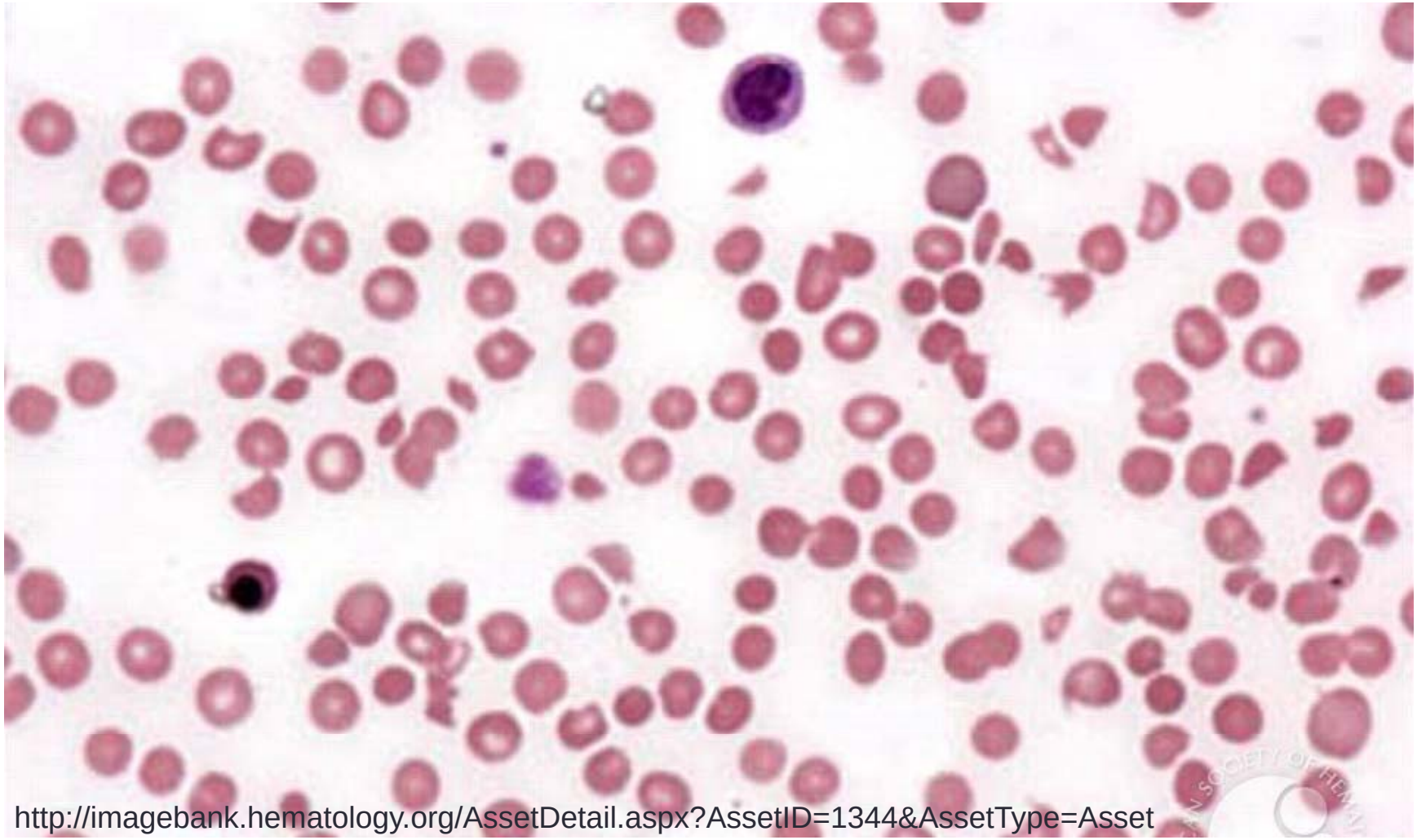
TTP

- 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



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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 10^9/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/m^2, 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/m^2) 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

- Scully M and Goodship T. How I treat thrombotic thrombocytopenic purpura and atypical haemolytic uraemic syndrome. *British Journal of Haematology.* 2014:**164**, 759-766.
- George JN. How I treat thrombotic thrombocytopenic purpura: 2010*. Blood.* 2010: 116, 4060-4069.
- Bell et al. Improved Survival in TTP-HUS. *New England Journal of Medicine.* 1991;325(6):398-403.
- Scully M et al. Guidelines on the diagnosis and management of thrombotic thrombocytopenic purpura and other thrombotic microangiopathies. *British Journal of Haematology.* 2012, 1-11.
- George JN. Acquired TTP: Initial Treatment. www.uptodate.com. Accessed Nov. 1, 2015.
- George JN. Acquired TTP: Clinical Manifestations and Diagnosis. www.uptodate.com. Accessed Oct. 30, 2015.
- Kaplan AA, Fridey JL. Therapeutic apheresis (plasma exchange or cytapheresis): Complications. www.uptodate.com. Accessed Nov. 1, 2015.