Scary Platelet Syndromes – Dealing with Evil 3 Letter Acronyms

Mayo CME Acute Care Course for NPs and PAs

Scottsdale, Arizona  Rochester, Minnesota  Jacksonville, Florida

Joseph Mikhael, MD, MEd, FRCPC, FACP
Associate Dean, Mayo School of Graduate Medical Education
Professor of Medicine, Mayo Clinic Arizona
Disclosures

• None
Objectives

• Review a case of thrombocytopenia admitted to hospital
• Outline the features of microangiopathic hemolytic anemia and its differential diagnosis
• Discuss the pathophysiology of TTP and HUS
• Provide an approach to the accurate diagnosis an initial management of patients with TTP
• Differentiate TTP from other similar conditions
• Prove that benign hematology may not be so benign...
Case

• 27 year old female with minimal PMH
  • Presents to family doc with fatigue
  • No bleeding, bruising
  • Afebrile, clinically stable, but appears jaundiced
• Labs
  • Hb 8.7 (MCV 104), WBC 4.8, Plts 47
  • Iron studies normal
  • Creat 0.6, Tbili 3.2
• Abdo US pending
Case Contd

- What will you do next?
Case contd.

- Phone call made to Hematologist
  - Blood smear
  - Reticulocyte count
  - Fractionate Tbili, LDH, haptoglobin

- Pt sent to ER...
Case contd.

• Hospital
  • Remains afebrile, hemodynamics stable, exam normal except for jaundice
  • Hb 8.0, plts 28
  • Tbili 3.8 (all indirect)
  • LDH 890
  • Cr 0.7
  • Smear – 5-7% fragmentation
  • Retic 0.099, (5%)
Case contd.

• What is your diagnosis?
• Differential diagnosis?
• Other tests?
• Initial management?
Love Your Platelets

- Recall the role and importance of platelets in primary hemostasis
- Be aware of impaired plt function - esp secondary to drugs
  - Reversible (NSAIDS – ½ life of drug)
  - Irreversible (ASA – life of platelet)
- Approach to low plts is diverse:
  - Reduced production
  - Enhanced destruction
  - Increased sequestration
- Recall inpatient platelet pearls
  - HIT – timing (5-15 days), depth of drop (50%) but rarely < 20, False positives (20% positive in ICU even without heparin)
  - DIC – prolong PT/PTT, underlying cause
Thrombocytopenia – 7 Important Questions

1. Is it sustained?

*Low plts very common transiently, especially with infections and meds*

2. Has the patient had a recent infection?

*May cause the low/high plts, but may also be consistent with concomitant ITP*

3. Is the patient taking any meds that cause low plts?

*What drug doesn’t? Common culprits include heparin, antibiotics, quinine, VPA and sulfa drugs*
Thrombocytopenia contd.

4. Does the patient have evidence of a platelet consumption syndrome?

*Are they sick? Are they also anemic? New renal insufficiency? Must rule out DIC & TTP*

5. Is there other evidence of an immune disorder?

*do they have RA, SLE or other auto-immunity?*

6. Does the patient have chronic liver disease?

*Hypersplenism is likely under-recognized cause – even mild/moderate alcohol use can*
7. Is the patient bleeding or not bleeding out of proportion to platelet count?

*ITP patients tend not to bleed, should also consider coagulation defect (von Willebrand’s disease) if atypical*
Microangiopathic Hemolytic Anemia (MAHA)

• A critical process to understand

• Definition
  • NON immune (ie DAT negative) hemolysis
  • Fragmentation

• Has limited DDx that is valuable to remember
Fragmentation
Take Home Message # 1

- PLEASE remember to order a blood smear (film) and a reticulocyte count when evaluating a patient with anemia
  - Cheap
  - Fast
  - Highly diagnostic
  - Identifies “scary” conditions
MAHA - DDX

- TTP-HUS spectrum
- DIC
- Valves, lines, grafts...
- Malignant Hypertension
- HELLP
- Vasculitis
- Scleroderma renal crisis
- Drugs
- ? Malignancy/post transplant
Take Home Message #2

• Understand the importance of recognizing MAHA and its DDx
Thrombotic Thrombocytopenic Purpura (TTP)

- A multisystem disease characterized by MAHA and thrombocytopenia
- Similar in clinical presentation to HUS (hemolytic uremic syndrome)
- These 2 diseases are somewhat different in adults and children
- HUS has prominent renal insufficiency (and often less thrombocytopenia)
- HUS more likely associated with shiga toxin (e coli 0157:H7)
TTP

• Recall not so “classic” pentad
  • MAHA
  • Thrombocytopenia
  • Fever
  • Renal insufficiency
  • Neurological symptoms

• Rare to find all anymore – top 2 most NB
Take Home Message #3

• TTP-HUS must be considered in pts with MAHA and thrombocytopenia alone
Recall the role of vonWillebrand's factors

“unusually large” VWF broken down by ADAMTS13 (a cleaving protease)

Decreased ADAMTS13 – either due to genetic absence or acquired inhibitor accounts for some of the disease

NB: testing for ADAMTS13 PROGNOSTIC and DIAGNOSTIC – note “new” diagnosis of atypical HUS
TTP - Associations

• HUS – e coli 0157:H7 shiga toxin
  • Bloody diarrhea hallmark (but not concretely diagnostic)

• Pregnancy
  • May be first presentation of TTP, or exacerbate known TTP

• Drugs: mitomycin, ticlopidine, quinine…newer immune agents (esp “limus”)
TTP – Clinical Features

• MAHA
  • Fragments (schistocytes) usually greater than 1% - possible less at relapse
• Hemolysis
  • Elevated retic
  • Elevated indirect bili
  • Low haptoglobin
  • High LDH – good marker to follow
TTP – Features contd.

• Thrombocytopenia
  • Platelet activation from endothelial injury without coagulation cascade upregulation
  • Usually less than 50, often even lower
  • Not as prominent with HUS
  • Bleeding not usually a prominent feature
TTP – Features contd.

- Renal insufficiency
  - Worse in HUS
  - Secondary to thrombotic microangiopathy
  - May require dialysis

- BUT a kidney biopsy showing microangiopathy does not = TTP!
TTP – Features contd.

• Neurological symptoms
  • Headache and confusion most common
  • May be focal
  • May be as severe as grand-mal seizures
  • Possible PRES (Posterior reversible encephalopathy syndrome) on imaging
  • Hallmark is reversibility
TTP - Features contd.

- Fever
  - Usually low grade
  - Mechanism not well understood
  - If high spiking, consider sepsis

- Cardiac
  - More recognized of late
  - microthrombi
TTP – What it is NOT

- DIC
- Sepsis
- Vasculitis
- Scleroderma renal crisis
- Antiphospholipid antibody syndrome (APLA)
- Heparin induced thrombocytopenia (HIT)
- Autoimmune hemolytic anemia (AIHA)
- Malignant Hypertension
- HELLP (Hemolysis, Elevated Liver enzymes, Low Platelet count)
- Malignancy
DIC

• Imbalance in the coagulation resulting in upregulation

• Like
  • MAHA and thrombocytopenia

• Unlike
  • Clinical setting of “sickness”
  • Prolonged PT and PTT
  • Low fibrinogen
  • Less prominent hemolysis
Sepsis

• Systemic inflammatory response to infection or direct toxin

• Like
  • Thrombocytopenia, possibly DIC
  • Often renal insufficiency, fever

• Unlike
  • Clinical setting
  • Hyperthermia, hypothermia
  • Other organ involvement, lactate
Vasculitis

• Inflammatory condition of vessels, often autoimmune – SLE, RA, other CTDz

• Like
  • Mild MAHA, thrombocytopenia
  • May have neuro involvement
  • May even have low ADAMTS levels

• Unlike
  • Usually known disease, plts not as low

*Note: may be most difficult to differentiate from TTP…?overlap syndrome*
Scleroderma Renal Crisis

- Renal manifestation of scleroderma with microangiopathy and hypertension

- Like
  - Renal failure, MAHA, thrombocytopenia
  - May have neuro involvement

- Unlike
  - Presence of autoantibodies
  - Therapy is control of hypertension
APLA

- Catastrophic APLA syndrome with micro and macrovascular thrombosis

- Like
  - Microvascular thrombi, possible consumptive thrombocytopenia

- Unlike
  - Prolongation of PTT by APLA
  - More obvious thrombosis
HIT

• Antibody directed against heparin-plt factor complex in response to heparin

• Like
  • Thrombocytopenia

• Unlike
  • No MAHA
  • Clinical context (5-15 days, plt drop 50%)

Note – please do not become HIT neurotic and order the test too often
AIHA

• Autoimmune hemolysis with positive DAT (warm or cold)

• Like
  • Hemolysis (but not MAHA)
  • Thrombocytopenia possible if with an associated condition (eg CLL)

• Unlike
  • Not MAHA (DAT vs fragments)
  • Rare neuro, renal or fever

*Note: highlights importance of smear and DAT*
Malignant Hypertension

• Uncontrolled hypertension, diastolic usually over 130, papillary changes

• Like
  • May have MAHA

• Unlike
  • HTN prominent, not usually thrombocytopenic
  • Context of poorly controlled HTN
HELLP

• Pregnancy associated condition with or without eclampsia

• Like
  • MAHA, possible post partum renal failure

• Unlike
  • More like widespread DIC with sepsis
  • TTP less likely immediately postpartum
Malignancy

• Previously untreated malignancy can have associated MAHA, possibly tissue factor related (often adenocarcinoma)

• Like
  • MAHA, systemically unwell, thrombocytopenia

• Unlike
  • Other features consistent with malignancy
  • Note: usually not considered until therapy for TTP fails
Take Home Message #4

- Differentiating TTP from similar conditions is critical to diagnosis and initial management
TTP - Management

- Immediate and accurate diagnosis
- Plasma exchange is mainstay of therapy
  - Replace absent ADAMTS13 protease
  - Dilute ADAMTS13 inhibitor
  - Targets: plt up (150), LDH down, fragments down
- PLEX usually daily for 5 days then taper based on clinical scenario
Take Home Message #5

- Plasma exchange is critical therapy in this life threatening condition and should be instituted as soon as possible
TTP – Management contd.

• Important Caveats
  • If PLEX not available, plasma infusion can temporize
  • DO NOT
    • Antiplatelet agents
    • Platelet transfusions
  • Addition of steroids to PLEX routine if response not optimal
  • Role of rituximab unclear, usually in relapsing/refractory disease... but now may be seen more in upfront therapy

*Note: disease may be atypical at relapse*
Back to the case…

• Patient appropriately diagnosed with TTP
• Started on PLEX, steroids added day 3
• By day 5 plts to 173, LDH 200, fragments less than 1%
• ADAMTS13 testing revealed presence of inhibitor
• No evidence of relapse 22 months later…😊
Case #2 - Ms. Equivocal

63 yo retired CEO of Yes-No-Maybe.com

- Lives in Wyoming (summer), New York (fall) AZ (winter) and North Carolina (spring)
- History of IBS, paroxysmal Afib
- Presents for annual physical
- CBC normal but platelet count is 89 (last year was 104, year prior 198)
Case #2 Lessons

• She has an evolving thrombocytopenia that possibly signify ITP

• Check meds, etoh intake, general health

• Ensure rest of CBC is normal

• Plan to repeat in 3-4 month intervals

• If further trend to near 50 range, call heme…
Case # 2 Lesson – ITP
(Immune Thrombocytopenia)

- Key Updates:
  - No longer “idiopathic”
  - Fatigue known effect of low plts
  - 30 is the new 50 (some think 20 is the new 30!)
  - Mechanism also includes reduced production
  - Major treatment options include steroids, splenectomy, rituximab and thrombopoietic agents
Case #3 - Mr. M. D. Esther

78 yo man CEO of ALLDOWN.com

- History of CAD, vascular dz, chronic renal insufficiency and osteoarthritis
- Fatigue slightly worse in last 3 months
- No appreciable findings on exam
- CBC: Hb 10.3, WBC 3.9, Plts 47 (MCV 107) – trend has seen plts dropping and MCV climbing
Case #3 Lessons

- Want to know about ETOH intake and or liver disease
- Pattern fits evolving MDS (myelodysplasia)
- Different than the “Anemia of Aging”
- Key measure is Hb as goals in this age group is transfusion avoidance/reduction
- Newer agents being developed with less toxicity
Conclusions

1. PLEASE remember to order a blood smear (film) and a reticulocyte count when evaluating a patient with anemia

2. Understand the importance of recognizing MAHA and its DDx

3. TTP-HUS must be considered in pts with MAHA and thrombocytopenia alone

4. Differentiating TTP from similar conditions is critical to diagnosis and initial management

5. Plasma exchange is critical therapy in this life threatening condition and should be instituted as soon as possible