General Hematology!

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Disclosures

• None
Today

- Abnormal MRI signal
- TTP update
Abnormal MRI Signal

• Common issue
• Scary for patients
• Absolutely no guidance or consensus
• An approach
Bone Marrow 101

- “Red marrow” produces blood
- Percent of red marrow decreases with age and replaced with fat “yellow marrow”
- Red and yellow marrow different on MRI
What can go Wrong?

• Variation in regression of red marrow
• Physiological responses to physiologic stresses
• Bad things
Variation in Regression

- Conversion may not be uniform
- Can be “speckled pattern”
- Usually recognized as normal variant
Smokers

• Smoker have increased hematopoesis
  – Inflammation
  – Carbon monoxide

• Can see abnormal marrow MRI
Obesity

• High WBC very common
  – Adipose cells secrete growth factors
  – WBC 10-18,000

• Can see reconversion

• Reverses with weight loss
Exercise

- Increased red cell turnover
  - Hemolysis
  - Iron deficiency
- Reconversion near joints
  - Also with DJD
Anemia

• Can lead to a variety of abnormalities
• Iron/B12 deficiency
  – Increased reconversion
• Aplastic anemia
  – All fat
• Recent IV iron
Radiation

- Radiation therapy can permanently destroy marrow
- Can be very remote
  - Childhood cancer
  - Adjuvant breast cancer
POST RADIOTHERAPY CHANGES

Post RT, tumour/normal marrow is replaced by fat which is high signal on T1

Sharp cut off in signal change where RT effect ends
Bad Things

- Leukemia
- Marrow fibrosis
- Myeloma
- Lymphoma
Leukemia

- Hypercellular – very abnormal MRI signal
- CBC always abnormal
Discussion

- **Findings**
  - Diffuse low signal of bone marrow
  - T1 bone marrow signal darker than intervertebral discs

- **Differential**
  - Leukemia
  - Chronic anemia
  - Myelofibrosis
  - Lymphoma
  - Multiple myeloma
  - Diffuse metastases
  - “Red” hematopoietic marrow

http://headneckbrainspine.com/Case-335-discussion.php
Marrow Fibrosis

- Myelofibrosis
  - Myeloproliferative syndrome
- Secondary fibrosis
  - Lupus
  - Infections
  - Etc..
- CBC/smear abnormal
https://radiologykey.com/myelofibrosis/
Lymphoma

• Many types of lymphoma
• Marrow
  – Diffuse
  – Nodular
• Marrow only presentation unusual
https://radiopaedia.org/cases/lymphoma-of-the-spine-1
Myeloma

- Two patterns
  - Diffuse infiltration of plasma cells
  - Plasmacytomas
OK How do I work up the patient?
History

• Pattern of pain
  – Weeks vs year
• “B” symptoms
  – Night sweats
  – Weight loss
  – Fevers
• Smoker?
• Exercise?
• Job?
Labs

• How far to go?
• Informal poll of my colleagues
  – Ranged from only a CBC to deep genomic sequencing of marrow
Essential

- Complete blood count
- CMP
  - Renal (myeloma)
  - Total protein (myeloma)
- LDH?
Almost Essential

- Myeloma work-up (age > 40)
- Serum protein electrophoresis
- Serum – not urine – free light chains
Don’t do!

• Urine light chain  
  – Not standardize

• UPEP  
  – Not sensitive
Our Data

• 1500 spine MRI
• 4% abnormal marrow signal
• 1 myeloma

• Spine 15:390, 2020
When do I Marrow?

- Only if CBC or other testing suggest pathology
- Most are benign causes
- If in doubt – talk with radiologist!
The Future

- Standardized reporting
- Standardized work-up!
- Research study going on
Bottom Line

• Look at report
• Look at patient
• Look at labs
Thrombotic Microangiopathy

- Key diagnostic features
  - Microangiopathic hemolytic anemia
    - Schistocytes
    - Hemolysis
  - Thrombocytopenia
  - High LDH
  - End organ damage
The Pentad of TTP: Dead, Dead, Dead, Dead, Dead

- Thrombocytopenia
- MAHA
- Mental status changes: only seen in 40-50%
- Renal insufficiency: most often mild
  - Proteinuria most common
- Fevers: 20%
Other Abnormalities

- LDH elevations (>2-3x nl)
- Myocardial involvement
- Pulmonary involvement
- Gastrointestinal involvement
  - Pancreatitis
Pitfalls in Diagnosis

- Classic pentad most often not present
- Thrombocytopenia may be mild (20-60,000/ul)
- Neurological defects vague
- Diagnosis not thought of
## PLASMIC Score

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Result</th>
<th>Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet count</td>
<td>&lt;30K</td>
<td>1</td>
</tr>
<tr>
<td>Creatinine</td>
<td>&lt;2.0</td>
<td>1</td>
</tr>
<tr>
<td>INR</td>
<td>&lt;1.5</td>
<td>1</td>
</tr>
<tr>
<td>MCV</td>
<td>&lt;90</td>
<td>1</td>
</tr>
<tr>
<td>Presence of hemolysis variable</td>
<td>Either:</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>- Retic &gt; 2.5%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- Undetectable haptoglobin or</td>
<td></td>
</tr>
<tr>
<td></td>
<td>- iBili &gt; 2 mg/dL</td>
<td></td>
</tr>
<tr>
<td>Absence of active cancer</td>
<td></td>
<td>1</td>
</tr>
<tr>
<td>No prior stem cell or organ transplant</td>
<td></td>
<td>1</td>
</tr>
</tbody>
</table>

### PLASMIC score

<table>
<thead>
<tr>
<th>PLASMIC score</th>
<th>Probability of TTP</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>Low: &lt;5%</td>
<td>Close observation&lt;br&gt;Consider alternative diagnoses&lt;br&gt;Send ADAMTS13 testing if no alternative cause identified</td>
</tr>
<tr>
<td>5</td>
<td>Intermediate: 5–25%</td>
<td>Send ADAMTS13 testing&lt;br&gt;Obtain expert consultation&lt;br&gt;Consider plasma infusion&lt;br&gt;TPE if no other cause identified</td>
</tr>
<tr>
<td>&gt;5</td>
<td>High: 60–80%</td>
<td>Send ADAMTS13 testing&lt;br&gt;Obtain expert consultation&lt;br&gt;Immediate TPE if high clinical suspicion for TTP</td>
</tr>
</tbody>
</table>

Abbreviations: TMA, thrombotic microangiopathy; TTP, therapeutic plasma exchange; TTP, thrombotic thrombocytopenic purpura.

*Quantitative risk estimates based on approximate probabilities observed in the PLASMIC derivation and validation cohorts.*
ADAMTS 13 Levels

• Levels may guide therapy
• <5% and inhibitor
  – More severe disease but lesser risk of death
  – Strong role for immunosuppression esp if relapses
• <5% and no inhibitors
  – Congenital?
• 5-50%
  – Many diseases
• Normal
  – Think aHUS
Therapy

- Steroids
- Plasma exchange
- Caplacizumab (?)
- Immune globulinin (??)
- Vincristine
- Rituximab
- Splenectomy
Steroids

- Seems to play a role in TTP therapy
- Usually 60-120 mg prednisone
- Slow taper when patients responds
- Some patients steroid sensitive
Plasma Exchange

- Key factor in outcome
  - 2 RCT
- Start with 1.5 plasma volume exchange for at least 5 days
- Follow LDH
- Taper when LDH normal
- Plasma infusion until exchange
  - 1 unit/4-6 hours
Caplacizumab

- Block VWF from binding platelets
- Decreases LOS and ICU stays
- Started at diagnosis and given until ADAMTS13 > 10%
TTP: Role of Von Willebrand's Factor

• VWF mediates binding of platelets to endothelium
• VWF synthesized as giant molecule and is cleaved to a large molecule
• Metalloprotease is responsible for cleaving VWF
  – ADAMTS13
anti-vWF Nanobody
90% homologous to human germline
128 aa

3 x alanine linker

anti-vWF Nanobody
90% homologous to human germline
128 aa
HERCULES

• DBRCT  N = 145
• Caplacizumab 10mg IV before plex then 10mg sq for 30 days
  – Could be extend by 28 days if ADAMTS13 < 10% at the end of 30 days
• Primary Endpoint Plts > 150,000
• NEJM 380:335-46, 2019
Results

• Cap resulted in greater plt response (1.55)
• Relapses (after treatment ended)
  – C: 9 (12%) P: 28 (38%)
• Days of Plex (mean/median)
  – C: 5.8/5  P: 9.4/7.0  (-3.6/2.0)
• Hospital days
  – C: 9.9/9.0  P: 14.4/12.0  (-4.5/3.0)
• ICU Days
  – C: 3.4/3.0  P: 9.7/5.0  (6.4/2.0)
Other Endpoints

- Deaths C:1 P:3
- Serious Bleeding C:11% P:1%
  - One patient treated with VWF
- More minor bleeding
  - Gums/nose
ADAMTS13

• 1 week after end of plex 57% still had ADAMTS13 < 10%
• 24% still low after trial ended
• Low levels predicted relapse
<table>
<thead>
<tr>
<th>Efficacy endpoints</th>
<th>Caplacizumab (N=108)</th>
<th>Placebo (N=112)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary endpoint</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Time to platelet count response&lt;sup&gt;b&lt;/sup&gt;: caplacizumab vs. placebo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Platelet count normalization ratio (95% CI)</td>
<td>1.65 (1.24-2.20)</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.0006</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary endpoints</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>The proportion of subjects with at least one of the events below while on DB/SB study drug treatment – no. (%)</td>
<td>14 (13.0)</td>
<td>53 (47.3)</td>
</tr>
<tr>
<td>TTP-related death</td>
<td>0</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>major thromboembolic event&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 (7.4)</td>
<td>14 (12.4)</td>
</tr>
<tr>
<td>TTP recurrence (exacerbation)&lt;sup&gt;c&lt;/sup&gt;</td>
<td>6 (5.6)</td>
<td>39 (34.8)</td>
</tr>
<tr>
<td>P value</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>TTP recurrence during the entire study period&lt;sup&gt;f&lt;/sup&gt; – no. (%)</td>
<td>19 (17.6)</td>
<td>39 (34.8)</td>
</tr>
<tr>
<td>P value</td>
<td>0.0040</td>
<td></td>
</tr>
<tr>
<td>Refractory to treatment&lt;sup&gt;d&lt;/sup&gt; – no. (%)</td>
<td>0</td>
<td>7 (6.3)</td>
</tr>
<tr>
<td>P value</td>
<td>0.0089</td>
<td></td>
</tr>
<tr>
<td>Mortality rate – no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>During the DB/SB treatment period</td>
<td>0</td>
<td>4 (3.6)</td>
</tr>
<tr>
<td>P value</td>
<td>0.0477</td>
<td></td>
</tr>
<tr>
<td>During the entire study period</td>
<td>1 (0.9)&lt;sup&gt;f&lt;/sup&gt;</td>
<td>5 (4.5)&lt;sup&gt;f&lt;/sup&gt;</td>
</tr>
<tr>
<td>P value</td>
<td>0.1086</td>
<td></td>
</tr>
<tr>
<td>Number of days of Plasma Exchange during the DB/SB treatment period&lt;sup&gt;d&lt;/sup&gt; – Mean (± Standard Deviation)</td>
<td>6.5 (4.5)</td>
<td>10.4 (7.7)</td>
</tr>
</tbody>
</table>
Conclusion

• Caplacizumab raised the platelet count quicker, lower the rate of relapse, and saved resources
Good

- Clearly reduced intensity of care
- Did reduce relapses
  - Higher incidence of late relapses
- Suggestive reduction of deaths/thrombosis
Bad

• Daily therapy for 30-58(?) days
• Need for addition therapy if ADAMTS13 is still low
• Expensive
• Incremental gain
• Studies low use of rituximab
Caplacizumab

- We use
  - Severe disease (neuro changes)
  - Refractory cases
Other Therapies

- IVIG: not effective
- Vincristine: classic drug for resistance disease
  - 2 mg day 1, 4, 7, 10
- Rituximab – lessens relapses
  - + Antibodies
Pre-emptive Therapy

• Check ADAMTS13 q3-6m in remission
• If < 10% - rituximab
Work-Up of TM

• Pre-treatment
  – ADAMTS13 levels and inhibitors
  – C3 and C4
• Consider congenital TTP
  – Very low ADAMTS13
  – No inhibitor
• Consider aHUS
  – ADAMTS13 normal
  – Family history of aHUS
  – Progressive disease – esp renal
The Nightmare Call

• “I have a pregnant patient who I think has TTP”
DDx

- Gestational thrombocytopenia
- Immune thrombocytopenia
- Microangiopathic hemolytic anemias
- HELLP syndrome
- Other bad pregnancy things
- Hypersplenism
Pregnancy Thrombocytopenia

- Very common
  - 1-2% of pregnancy
- Drop in platelet count normal
  - Increase M-CSF
  - Increase platelet turn-over
Gestational Thrombocytopenia

- Most common
- Counts slowly fall during pregnancy
- Nadir 50,-70,000/ul
- No harm to child or mom
- Normal counts outside of pregnancy
Immune Thrombocytopenia

- Relativity common
- Severe thrombocytopenia 1st trimester
- Can be exacerbation of ITP or de novo
- Mother presents with mucocutaneous bleeding
- Small risk child can have low counts due to passage of antibody
ITP: Diagnosis

• Clinical diagnosis!!!
• No other blood abnormalities
  – Review blood smear
• No suspect drugs
• Patient otherwise healthy
• No value in antibody test
• Bone marrow only for uncertain cases
Microangiopathic Hemolytic Anemias

• TTP most common in 2nd trimester
• Thrombocytopenia + hemolysis + end organ damage
• Plasmapheresis is treatment of choice
  – Can control disease throughout pregnancy
• Post-partum HUS
  – Devastating syndrome
    • ~ 100% renal failure untreated
Pregnancy TTP

- Tx: Plasma exchange daily and then taper
- May need to do throughout pregnancy
- Risk of recurrence with next pregnancy is ~30%
- Can be presentation of congenital TTP
HELPP syndrome

- Usual late in pregnancy
- Early HELLP seen with APLA syndrome
- Requires ending of pregnancy
How to Differentiate

• HELLP can have renal disease and schistocytes
• HELPP can persist post-partum
• Can see liver involvement in TTP and rarely aHUS
• All can have HTN
HELP Syndrome vs. Atypical Hemolytic Uremic Syndrome (aHUS) in the Postpartum Period

Postpartum Laboratory Evaluation
- Hemoglobin (Hgb)
- Platelet Count (Plt)
- Creatinine (Cr)
- Lactate Dehydrogenase (LDH)

Optimal Thresholds to Diagnose aHUS
- Hgb ≤ 8.5 g/dL
- Cr ≥ 1.9 mg/dL
- Plt ≤ 45 k/μL
- LDH ≥ 1832 U/L
-Cr ≥ 1.9 mg/dL + LDH ≥ 600 U/L

More than 95% specific for aHUS

Kidney Function
- HELP: usually begins to improve within 72 hours postpartum
- aHUS: usually progresses to severe kidney failure, often necessitating dialysis or complement inhibition

Take-Home Message
Pregnancy-associated aHUS should be considered when there is persistent hemolysis and renal failure in the postpartum period.
Talk

• Abnormal MRI marrow
  – Rare to be an issue
• TTP – still vexing