Hematologic Complications (of Autoimmunity)

KRISTINA HOOL, MD
ACP MONTANA CHAPTER CONFERENCE
29 MARCH 2019
Presentation Overview

- Introduction/background
- Immune-mediated thrombocytopenia
- Autoimmune hemolysis
- Autoimmune neutropenia
- Antiphospholipid antibodies and syndrome
Abnormal immune regulation and persistent inflammation are hallmarks of autoimmune disease/CTD

Hematologic abnormalities affecting one or more cell lines are common manifestations of autoimmune disease and can be reflective of disease activity

There is also a relationship between chronic immune dysregulation and lymphoproliferative disease, likely reflecting chronic activation and resultant proliferative drive
Autoimmune Thrombocytopenia

Case 1:

HO is a 22 year old student. You are called by student health when he presents with bruising and rash and is found to have profound thrombocytopenia.

Labs show a platelet count of 6k. WBC and Hb are normal. There are no renal, electrolyte or hepatic function abnormalities.

Physical exam demonstrates petechial rash and scattered bruising (pictured).
Peripheral Smear Review

Autoimmune Thrombocytopenia

- Anti-platelet autoantibodies are sent. They are negative for IgG and IgM.
- He is sent to the ER for evaluation and management. He feels well.

- What workup do you think that he needs?
- What is the most likely diagnosis? How can you prove it?
- Is it acceptable to give therapy with negative anti-platelet antibody testing?
- What initial treatment would be best?
ITP: Diagnostic Workup

- ITP really does remain a clinical diagnosis and a diagnosis of exclusion.
- Treatment is often empiric when ITP is the most likely diagnosis.
- Guidelines for workup focus more upon evaluation for ITP triggers than proof of ITP diagnosis.
- Profound single-digit thrombocytopenia with other cell lines preserved is highly suspicious for ITP.

- How does anti-platelet autoantibody testing fit in to this workup?
ITP: Diagnostic Workup

- Anti-platelet antibody testing is able to detect anti-platelet autoantibodies (IgG or IgM). It will also quantify reticulated platelets.
- Sensitivity: 53% (optimistic)
- Specificity: > 90%

- If absent, having the result does you no good at all. If present, it is quite helpful.
- In reality, it will take 48 hours to return and you will need to treat prior to having results.

https://oncohemakey.com/thrombocytopenia-caused-by-immunologic-platelet-destruction/
ITP: Diagnostic Workup

- This list has gotten shorter over the years. Depending upon who you ask.

<table>
<thead>
<tr>
<th>American Society of Hematology</th>
<th>International Consensus Report</th>
<th>McMaster ITP Registry</th>
</tr>
</thead>
<tbody>
<tr>
<td>CBC</td>
<td>CBC</td>
<td>CBC</td>
</tr>
<tr>
<td>Peripheral Smear</td>
<td>Reticulocytes</td>
<td>Reticulocytes</td>
</tr>
<tr>
<td>HIV</td>
<td>Peripheral Smear</td>
<td>Peripheral Smear</td>
</tr>
<tr>
<td>Hepatitis B and C</td>
<td>HIV</td>
<td>HIV</td>
</tr>
<tr>
<td>Further testing determined by history and CBC</td>
<td>Hepatitis B and C</td>
<td>Hepatitis B and C</td>
</tr>
<tr>
<td></td>
<td>Immunoglobulins</td>
<td>Immunoglobulins</td>
</tr>
<tr>
<td></td>
<td>DAT</td>
<td>DAT</td>
</tr>
<tr>
<td></td>
<td>H. Pylori</td>
<td>H. Pylori</td>
</tr>
<tr>
<td></td>
<td>Bone Marrow Biopsy</td>
<td>Bone Marrow Biopsy</td>
</tr>
<tr>
<td></td>
<td>Blood Type</td>
<td>Blood Type</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ASH has issued guidelines for the management of ITP.

First-line treatment options include:

- Steroids: Prednisone taper or Dex pulse. Both are acceptable. It is important to note that time to onset of effect is not immediate.
- IVIG: This is fairly uniformly effective in ITP, so much so that many consider response to IVIG a loose confirmatory test. Time to onset hours.
- It is reasonable to use both simultaneously.
- The question of platelet transfusions
Case 1 Update:

- HO was treated with Dex 40mg daily x 4 days as well as IVIG 1g/kg x 2 days. His platelets were > 20k immediately after IVIG dose 1 and normalized within 48 hours.
- Unfortunately, 2 weeks later they again declined to < 20. He was re-treated with the same regimen with immediate response.
- 2 weeks later: Relapse.
- Re-treated with IVIG and Rituximab. Now 10 weeks post-Rituximab he is still IVIG dependent.
- Splenectomy pending.
Unfortunately, not all ITP cases are so clear and clean.

Case 2:

GR is 58 years old and in good health. Her PMD noticed a dip in platelets to 124 on her annual wellness labs 6 months ago. Repeat confirms the abnormality, and 3 months later they are 118.

She’s in the hospital for an elective surgery. Due to worry for potential worsening of platelet count, consult is requested.

She feels fine, and is having no bleeding or bruising.
What is a reasonable workup?

- Evaluation of thrombocytopenia (inpatient or outpatient) focuses upon impaired production, increased destruction, and sequestration.
- For GR:
  - Sequestration: Spleen is not palpable and not enlarged on imaging
  - Impaired production: No obvious myelosuppressive medications. HIV, Hepatitis and EBV testing are negative. ANA is negative. Because other cell lines are uninvolved, bone marrow evaluation is deferred.
  - Destruction: DIC labs are normal. Anti-platelet IgG testing is strongly positive.
While appealing, anti-platelet antibody testing is not reliable, is not timely, and should not alter diagnosis and management.

When present, the detected antibody does not accurately reflect disease activity.

ITP comes in various shapes and sizes, as does most autoimmune disease.
Autoimmune Hemolysis

Case 3:

AW is a 64 year old man with active hepatitis C. His current viral load is detected at multiple million copies. Being semi-homeless, he is found sleeping outside and appearing very pale and somnolent, and is brought to the emergency room.

Hemoglobin is 5.9 with MCV of 111. Platelets are normal and WBC is marginally elevated (neutrophilic predominance). Total bilirubin is 4.9 and LDH is 447. Haptoglobin is undetectable at < 10.
Autoimmune Hemolysis

Autoimmune Hemolysis

- His direct coombs test is notably positive for IgG but not for complement. The antibody identified is non-specific and referred to as a “pan-reactive warm autoantibody.”
Autoimmune Hemolysis

- Direct Coombs Results:
  - IgG: Positive
  - Complement: Negative
  - Antibody of unknown specificity is identified.

https://www.sciencedirect.com/topics/medicine-and-dentistry/coombs-test
Approximately 50% of patients with AIHA will have an underlying disorder that can explain the reason for hemolysis. These disorders are the focus of the workup. Reasonable first-line workup would include:

- Screening for plasma cell disorder (SPEP/IFE and light chains, Igs)
- HIV, HBV, HCV testing
- Autoimmunity screen
- CT CAP and lymphoproliferative disorder screening

Workup beyond that above is outside the scope of this conference, and would be consultation-based.
Autoimmune Hemolysis

Supportive Care
- Treat any underlying cause.
- Folate supplementation to meet the erythropoietic demand. Additional iron or MVI support likely also helpful.
- Transfusion: Full compatibility testing can take 6+ hours or longer, and fully compatible units may not be available. Transfuse if anemia is life-threatening.
- Thromboprophylaxis.

Direct Management
- Steroids
- Rituximab
- IVIG
- Splenectomy

Selection is driven by individual patient circumstances and unique contraindications.
Autoimmune Hemolysis

**Case 3 update:**

- AW was treated with prednisone 1mg/kg/day and transfused with best compatible blood. He quickly recovered to a hemoglobin of greater than 10.
- Likely as a result of steroids, his HepC viral load skyrocketed.
- He was tapered off of steroids and referred for Hep C therapy. He was not a candidate due to lack of abstinence.
- He has since been lost to hematology follow-up.
Case 4: KHS is a 58-year old female with longstanding RA, poorly controlled. She has been on methotrexate for decades. When she relocates to the area and finds a new rheumatologist, she is referred to you for an ANC of 300.

She reports that this has been an issue for years. She has never had febrile neutropenia or been hospitalized.

She does not have splenomegaly or take other suspicious meds. Her other cell lines are preserved.

Bone marrow biopsy shows mild dysplasia, so the methotrexate is stopped. Unfortunately, 3-4 weeks later her neutrophil count demonstrates no improvement.
Autoimmune Neutropenia

- Can occur in the setting of autoimmune disease. RA is the most typically associated, followed by SLE.
- The neutropenia can serve as a marker for disease activity, improving with disease control.
- Reasonable therapies include treatment of the underlying disorder, steroids, IVIG, and neupogen.
- Autoimmune neutropenia is uncommon. While the neutropenia is severe and worrisome, infection is not that common.
Case 5 update: She tested strongly positive for anti-neutrophil antibodies. Responds well to growth factor support.

Re-started on meds to control her symptomatic RA, in the hope that her ANC will improve.
Case 5: HL is a 19 year old female who gave birth to twins 12 weeks ago (after developing pre-eclampsia and delivering early). At 12 weeks post-partum she experienced chest pain and shortness of breath. She was admitted for large clot burden PE, pulmonary infarct, and hypoxemia.

Interestingly, at the time of admission she has unexplained transaminitis, although it’s relatively mild. She is placed on eliquis, but has minimal to no symptom improvement after 5 days of anticoagulation.

She did have one early pregnancy loss prior to her pregnancy with the twins. Her mother died of an unexplained myocardial infarction in her 20s when HL was a baby.
Antiphospholipid Antibodies

- 1-5% of the healthy general population will have detectable anti-phospholipid antibodies.
- This prevalence is remarkably higher in autoimmune disease.
  - ~25-45% of SLE patients will have APL antibodies
  - ~20% of RA patients will have APL antibodies
  - The 20-year thrombosis risk in these patients approaches 50%
- They can occur transiently, associated with medication or illness.

- So is having a detectable antibody enough?
Antiphospholipid Antibodies

- **ALTERED COAGULATION**
  - TF up-regulation
  - increased prothrombin activation
  - protein C and S dysfunction

- **IMPAIRED FIBRINOLYSIS**
  - elevation of PAI-1 activity
  - reduction of tPA activity
  - reduction of annexin A2 activity

- **ENDOTHELIAL DYSFUNCTION**
  - increased expression of adhesion molecules (E-selectin, VCAM-1, ICAM-1)

- **PLATELET DISORDER**
  - increased expression of GP IIb-IIIa
  - increased production of TXA2
  - increase of vWF levels

Antiphospholipid Antibodies

Antiphospholipid Syndrome Criteria
Sydney revision of Sapporo criteria 2006

<table>
<thead>
<tr>
<th>CLINICAL CRITERIA</th>
<th>LAB CRITERA</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>1. Vascular Thrombosis</strong></td>
<td>1. anti-Cardiolipin IgG / IgM</td>
</tr>
<tr>
<td><strong>2. Pregnancy Morbidity:</strong></td>
<td>2. anti–beta-2 glycoprotein I (GP1)</td>
</tr>
<tr>
<td>a) death of normal fetus at ≥ 10 wks</td>
<td>3. Lupus anticoagulant (LAC)</td>
</tr>
<tr>
<td>b) premature birth at ≤ 34 wks due to preeclampsia</td>
<td>- medium to - high titer</td>
</tr>
<tr>
<td>c) ≥3 consecutive abortions at &lt;10wks</td>
<td>- at least X 2 times</td>
</tr>
<tr>
<td>d) placental insufficiency at &lt; 34 wks</td>
<td>- 12 wks apart</td>
</tr>
</tbody>
</table>

https://www.slideshare.net/Drchitra/anti-phospholipid-syndrome-36428996
Antiphospholipid Antibodies

- What is the best way to approach this in the acute-care setting, given the timepoints needed for diagnosis?
- Will this affect our selection of anticoagulation or target drug levels?
Case 5 Update:

HL is placed on Coumadin. She improves sufficiently to be discharged home on oxygen.

In hematology follow-up, her transaminitis was drastically worse. She had a high-titer ANA. Her APS panel was triple positive and high-titer with a baseline PTT in the 60s without correction on mixing.

She was diagnosed with SLE and started on therapy. Repeat 12-week APS titers were just as abnormal as prior but she was clinically back to baseline.

Most recently, got unexpectedly pregnant on Coumadin and now has a third baby. Everybody did great.
Thank you for having me!

Special thanks to Carrie, the conference staff, and Dr. Hoge.