Hematologic Complications (of Autoimmunity)

KRISTINA HOOL, MD

ACP MONTANA CHAPTER CONFERENCE

29 MARCH 2019

Presentation Overview

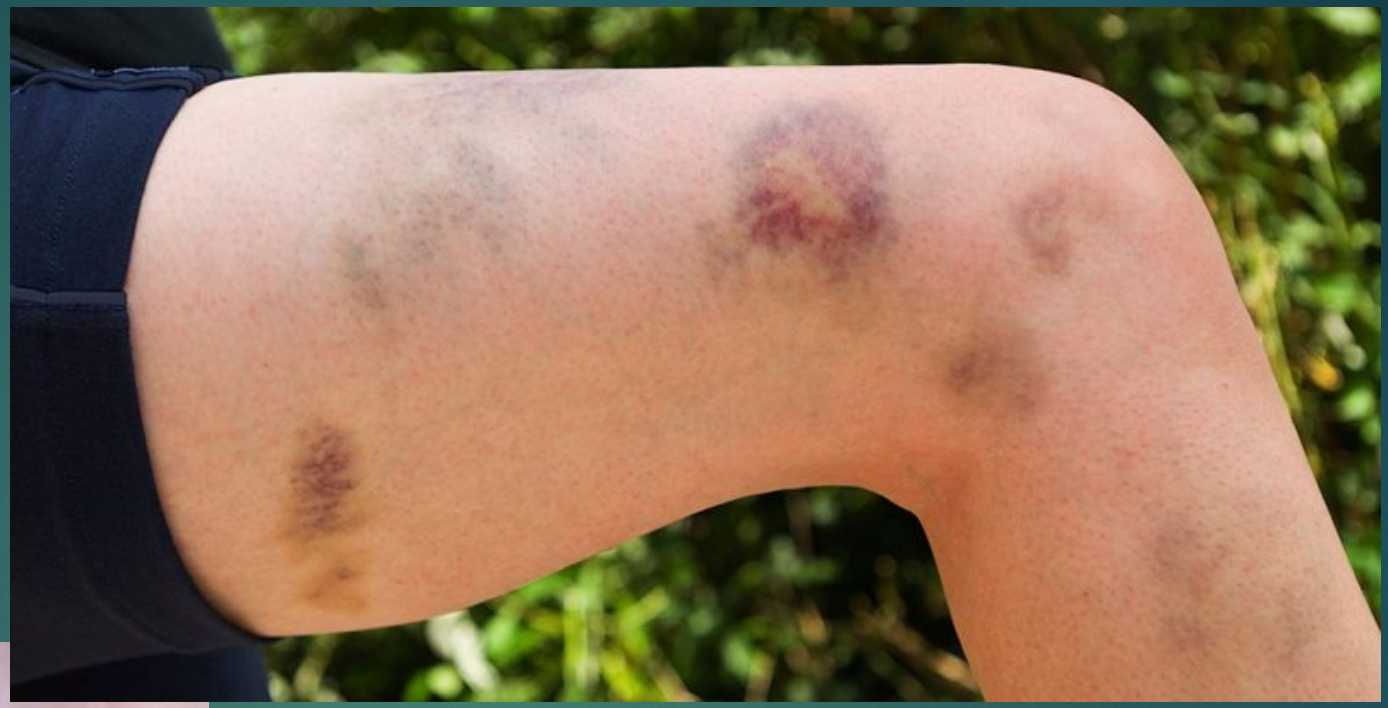
- Introduction/background
- Immune-mediated thrombocytopenia
- Autoimmune hemolysis
- Autoimmune neutropenia
- Antiphospholipid antibodies and syndrome

Introduction/Background

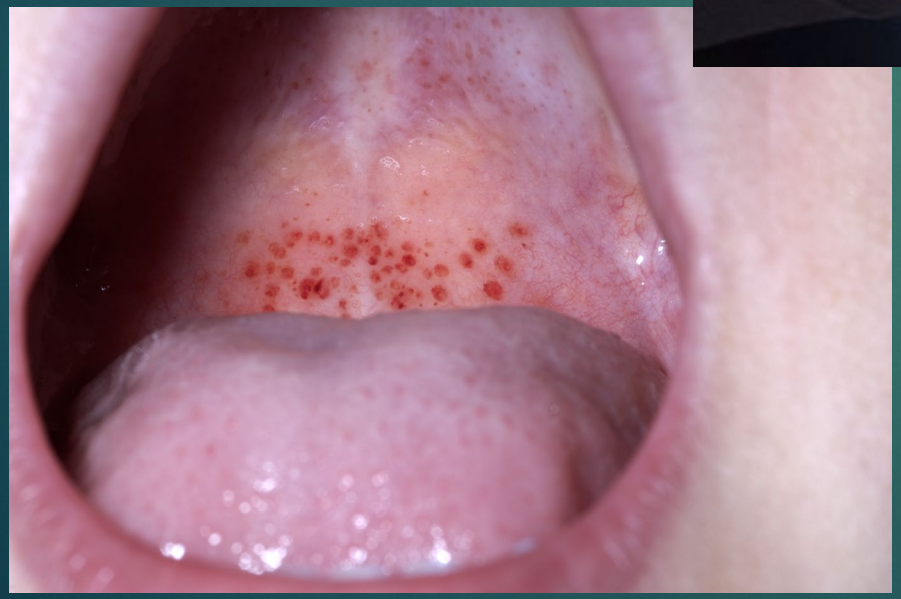
- Abnormal immune regulation and persistent inflammation are hallmarks of autoimmune disease/CTD
- Hematologic abnormalities affecting one or more cell lines are common manifestations of autoimmune disease and can be reflective of disease activity
- There is also a relationship between chronic immune 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).

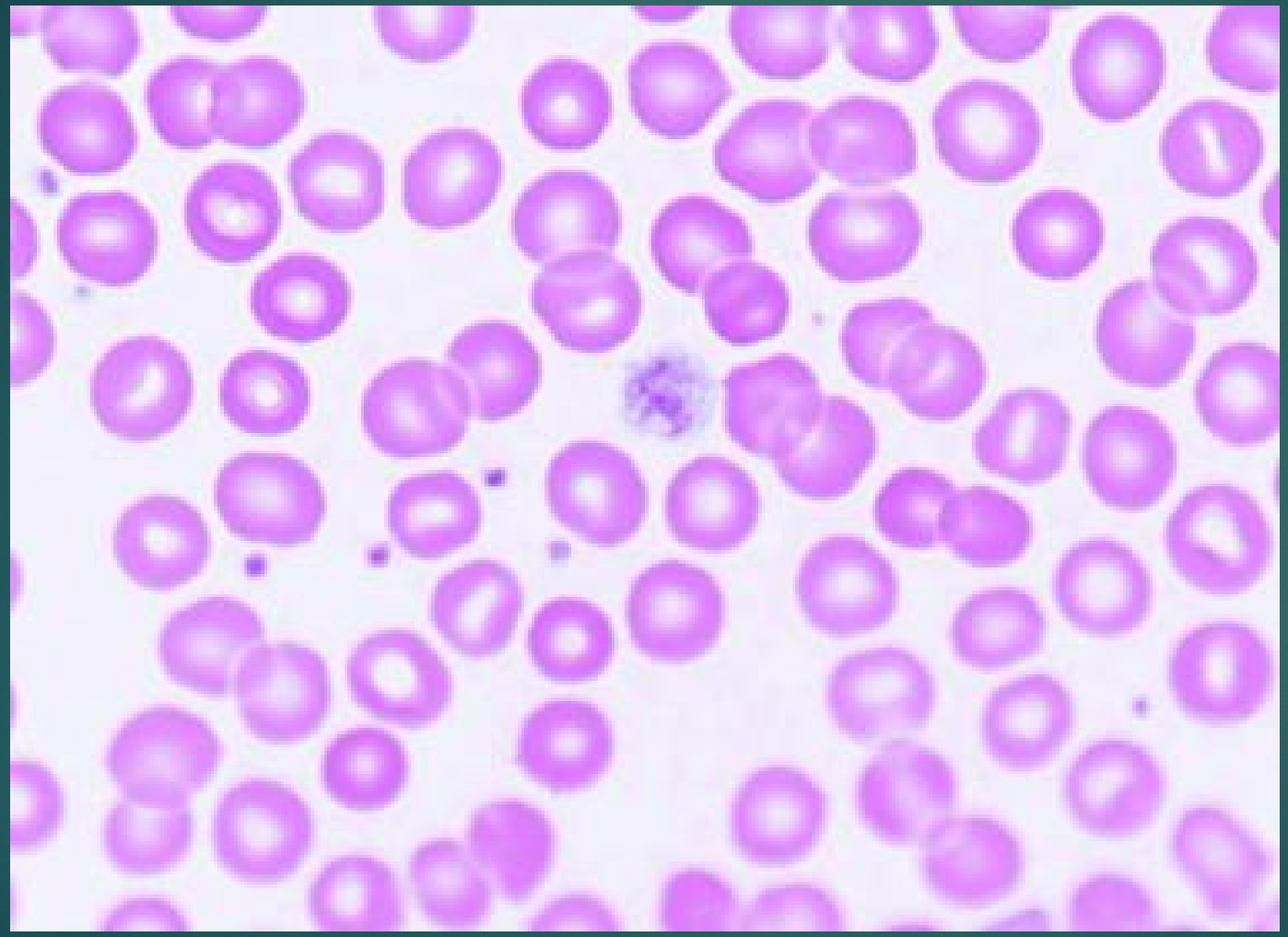


https://historycooperative.org/idiopathic-thrombocytopenic-pupura-a-history/



https://www.merckmanuals.com/en-ca/professional/hematology-and-oncology/thrombocytopenia-and-platelet-dysfunction/immune-thrombocytopenia-itp

Peripheral Smear Review



https://www.medscape.com/answers/201722-90176/202158-overview

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

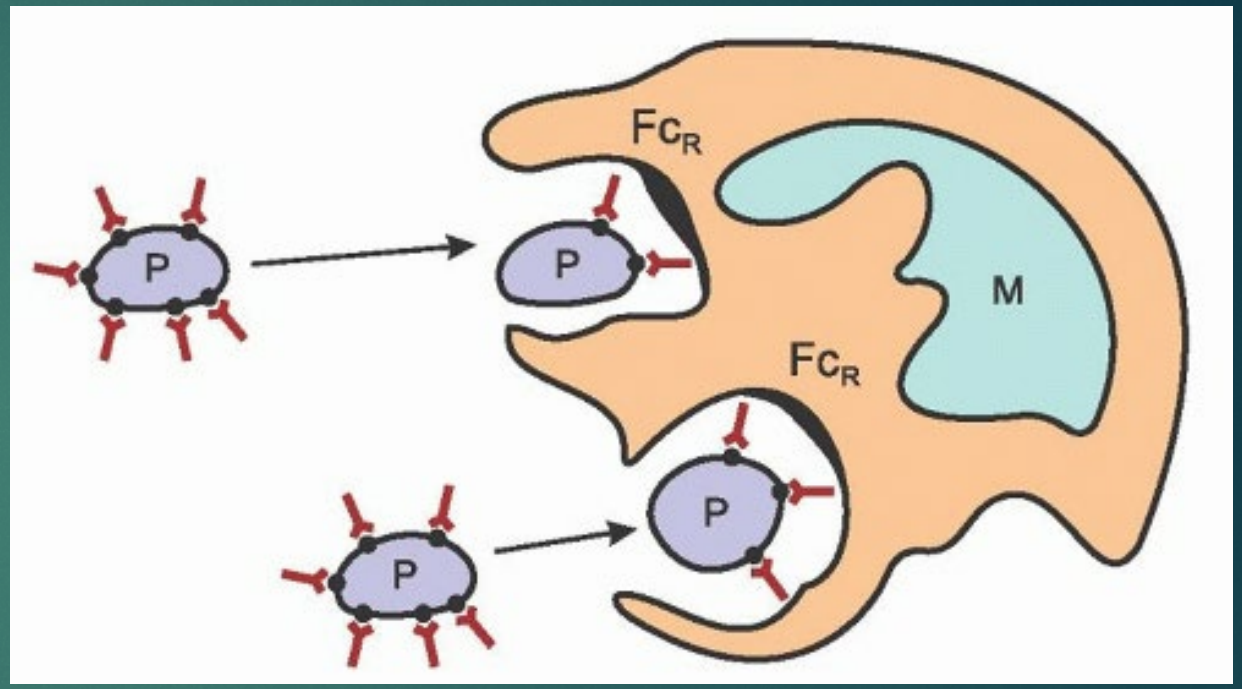
- ITP really does remain a clinical diagnosis and a diagnosis of exclusion.
- Treatment is often empiric when ITP is the most likely diagnosis.
- Guidelines for workup focus more upon evaluation for ITP triggers than proof of ITP diagnosis.
- Profound single-digit thrombocytopenia with other cell lines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

American Society of Hematology	International Consensus Report	McMaster ITP Registry
❖ CBC ❖ Peripheral Smear ❖ HIV ❖ Hepatitis B and C ❖ Further testing determined by history and CBC	❖ CBC ❖ Reticulocytes ❖ Peripheral Smear ❖ HIV ❖ Hepatitis B and C ❖ Immunoglobulins ❖ DAT ❖ H. Pylori ❖ Bone Marrow Biopsy ❖ Blood Type	❖ CBC ❖ Reticulocytes ❖ Peripheral Smear ❖ HIV ❖ Hepatitis B and C ❖ Immunoglobulins ❖ DAT ❖ H. Pylori ❖ Bone Marrow Biopsy ❖ SPEP ❖ TSH ❖ ANA, ACA, NSI ❖ Abdominal US

ITP: Initial Treatment Considerations

- 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.

Autoimmune thrombocytopenia

- 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.

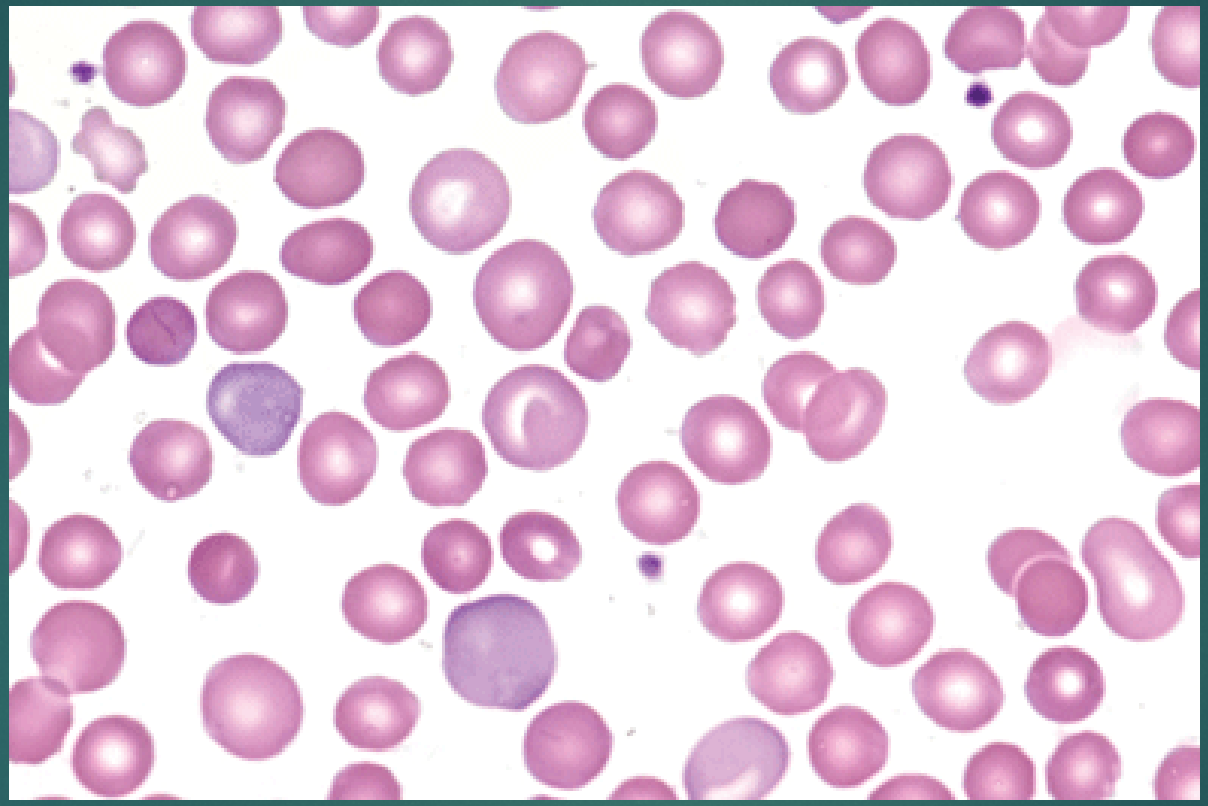
ITP Summary: A Cautionary Tale

- 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

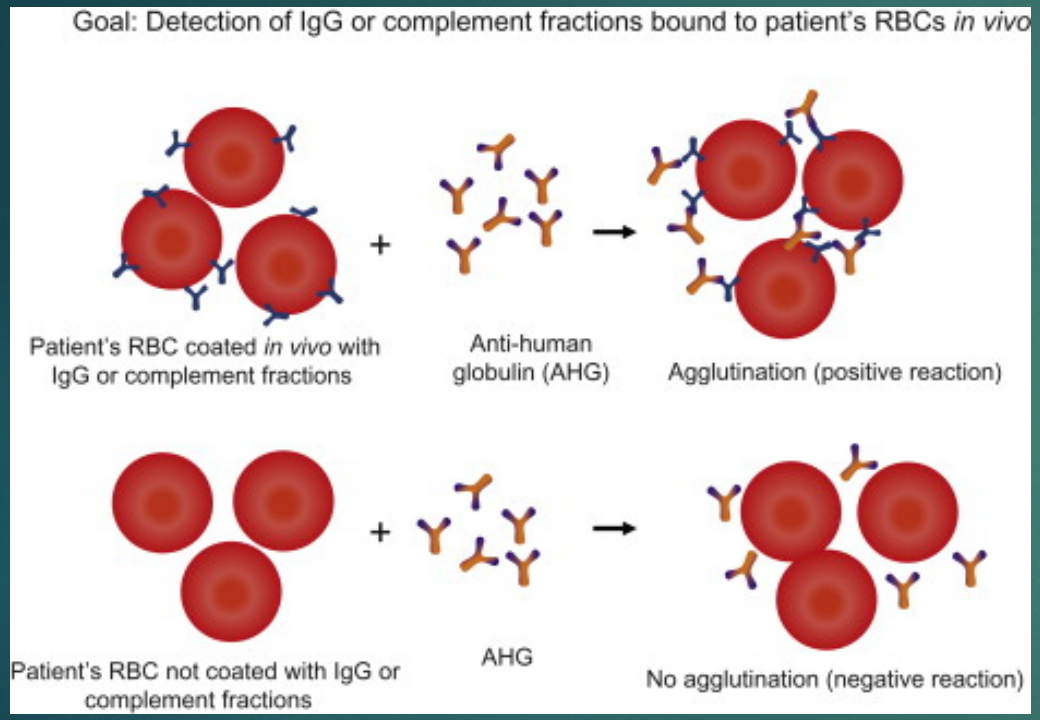


https://www.gponline.com/haematology-autoimmune-haemolytic-anaemia/haematology/anaemia/article/1118275

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



https://www.sciencedirect.com/topics/medicine-and-dentistry/coombs-test

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

Autoimmune Hemolysis

- 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.

Autoimmune Neutropenia

- **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.

Autoimmune Neutropenia

- **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.

Antiphospholipid Antibodies

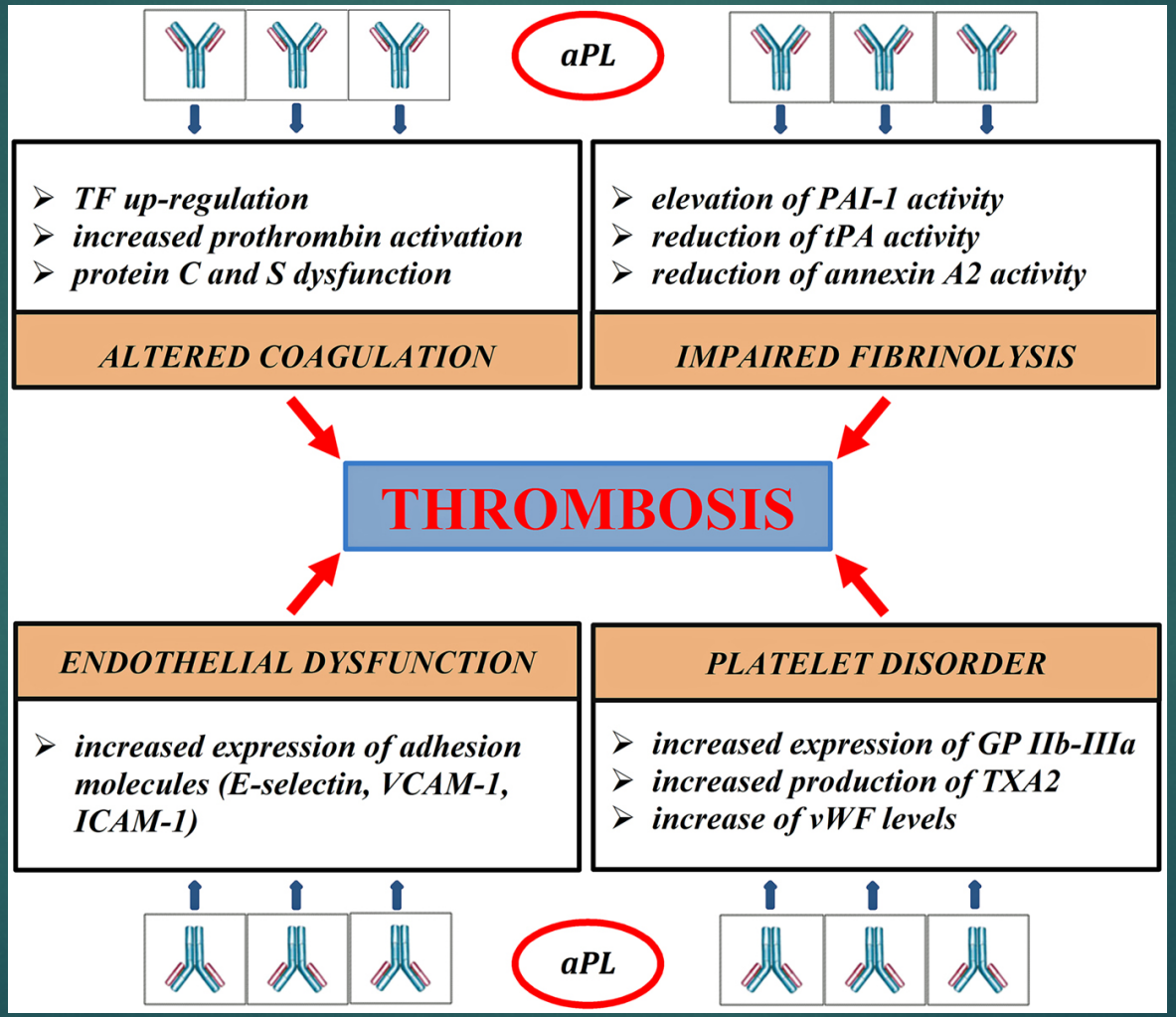
- **Case 5:** HL is a 19 year old female who gave birth to twins 12 weeks ago (after developing pre-eclampsia and delivering early). At 12 weeks post-partum she experienced chest pain and shortness of breath. She was admitted for large clot burden PE, pulmonary infarct, and hypoxemia.
- Interestingly, 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



https://www.frontiersin.org/articles/10.3389/fneur.2012.00150/full

Antiphospholipid Antibodies

Antiphospholipid Syndrome Criteria

Sydney revision of Sapporo criteria 2006

CLINICAL CRITERIA

1. **Vascular Thrombosis**

2. **Pregnancy Morbidity**:
   a) death of normal fetus at ≥ 10 wks
   b) premature birth at ≤ 34 wks due to preeclampsia
   c) ≥3 consecutive abortions at <10wks
   d) placental insufficiency at < 34 wks

LAB CRITERA

1. anti-Cardiolipin IgG / IgM
2. anti–beta-2 glycoprotein I (GP1)
3. Lupus anticoagulant (LAC)

- medium to - high titer
- at least X 2 times
- 12 wks apart

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?

Antiphospholipid Antibodies

- **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.

Questions/Comments

- Thank you for having me!
- Special thanks to Carrie, the conference staff, and Dr. Hoge.