Antiphospholipid Antibody Syndrome

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Disclosures

- None

Isn’t this a hematology problem?

Objectives

- Describe the clinical manifestations and pathogenesis of APS
- Describe the risk of thrombosis in patients with aPL
- Compare and contrast the management of venous and arterial APS
- Describe the implications of APS on family planning and management in pregnancy
- Apply evidence to choose the most effective anticoagulant for treatment of APS
- Evaluate a patient with features of catastrophic APS
Antiphospholipid Syndrome

- Original case series described by Graham Hughes in 1981
  - Arterial and/or venous thrombosis
  - Recurrent pregnancy loss
  - Thrombocytopenia

- Evolution of understanding of clinical spectrum
  - Asymptomatic presence of antibodies
  - Catastrophic multi-system organ failure
  - Primary or secondary to another autoimmune disease

Sydney Classification Criteria – 2006

From first VDRL test to APS

Disease Pathogenesis
Proposed Pathogenesis of Antiphospholipid-Antibody–Mediated Clinical Problems

1. Hemostatic reactions
   - Coagulation
     - Acquired protein C resistance
   - Fibrinolysis
     - Inhibition of tPA activity
     - Inhibition of fibrinolysis

2. Activated cellular elements
   - Endothelial cells
     - Proinflamm/prothrombotic phenotype
   - Monocytes
     - Induction of tissue factor, TLR4
   - Platelets
     - Activation of aggregation, LRP-8, GP1ba

3. Complement activation
   - Induction of thrombosis, activation of endothelial cells, proinflammatory environment
   - Placental inflammation/dysfunction and fetal loss

Case 1: +aPL and risk of thrombosis

Case

- 23 yo woman with SLE and “triple positive” aPLs asks you what her risk of developing a blood clot is. How do you counsel her about this risk?

Risk of first thrombosis in aPL carrier

- Prospective cohort of 98 aPL carriers
- Annual rate of first thrombosis 2.3% per patient-year (compared to 0.5-1/1000 per patient year in gen pop)
- 15-year 5% cumulative risk of first thrombosis ~30%

Risk of first thrombosis in aPL carrier

- Baseline characteristics were not predictive of first thrombosis, except a trend toward an increased risk with number of cardiovascular risk factors
- aPL profile at detection was not a predictor of first thrombosis


- aPL profile at the end of follow-up was more relevant than profile at detection in predicting the risk of first thrombosis
- Persistent aPL were significantly associated with an increased risk of first thrombosis
- Triple aPL positivity increased by three-fold the risk of first thrombosis


Assessing risk of thrombosis with aPL

- Stratify based on
  1. Antiphospholipid antibody profile: aPL type and titer
     - High risk: LA, "triple positive"
     - Moderate risk: +aCL, med-high titer
     - Low risk: isolated aCL or anti-B2GPI at low-med titer
  2. Antiphospholipid antibody profile: persistence of antibody
  3. Presence of other prothrombotic risk factors
     - Underlying SLE
     - Genetic prothrombotic
     - Traditional CV risk factors
     - Transient or acquired risk factors e.g. smoking, surgery, OCP
     - Comorbid conditions e.g. pregnancy, nephrotic syndrome

What is the actual risk of thrombosis with +aPL?

- According to clinical situation
  - Among patients with +aPL, the risk of developing thrombosis is:
    - <1% per year in otherwise healthy pts
    - Up to 10% per year in women with hx of recurrent fetal loss
    - >10% per year in pts with aPL and documented AC within 6 mos

- According to type of aPL
  - OR with +LA: VT 6.14, AT 3.58
  - Triple positive aPL: OR 33 for thrombosis (95% CI 7-157.6)

- Global APS Score (GAPSS): a composite score to predict complications
  - Predicts incidence of thrombosis better than aPL alone
  - Use for pts with SLE or +aCL, +aB2GPI, +anti-Phospholipid Antibody (LA, aCL, aB2GPI), +aPT/PS, +hyperlipidemia, +HTN, +smoking, +NF, +nephrotic syndrome
Case

- She wonders if there is anything she should do to reduce her risk of thrombosis. What do you recommend?

APLASA Study

- RCT of primary prevention in asymptomatic aPL+ individuals
- 98 patients with +LAC x 2 and/or +aCL x 2 (>20) randomized to ASA 81 or placebo
- Randomization stratified by low and high risk
- Followed for 2.3 +/- 0.95 years

APLASA Results

- No significant difference in risk of first thrombosis in aspirin group versus placebo group
- However:
  - Event rate was low overall
  - Low-risk group

Primary Prevention in APS

- Individual patient-level data meta-analysis
- Pooled data from 6 cohort studies of aPL carriers + 497 patients
- Were able to adjust for traditional CVD risk factors
- 2-fold reduction in risk of first thrombotic event in treatment group
Primary prevention in asymptomatic aPL patients without SLE

- **Low dose aspirin**: No prospective data support empiric therapy with LDA; major annual bleed risk increased from 0.007% to 0.10%
- **HCQ**: RCT terminated early
- Recommendation: LDA in aPL+ patients with high risk profile and/or presence of other thrombotic risk factors (benefit uncertain)
- Modify other risk factors such as HTN, HL, DM, avoid estrogens

APS Task Force (Ruiz-Iristorza et al, Lupus 2011;20:206.)

Primary prevention in asymptomatic aPL patients with SLE

- No prospective RCT supports use of ppx
- **LDA**: Observational studies suggest benefit
- **HCQ**: Observational studies suggest protective effect
- Recommendation: consider LDA and HCQ in mod-high aPL+ SLE patients
- Modify other risk factors such as HTN, HL, DM, avoid estrogens

APS Task Force (Ruiz-Iristorza et al, Lupus 2011;20:206.)

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Case 2: Treatment of thrombotic APS

- 34 yo woman with SLE presents with L MCA stroke. She is found to have +LAC by RVVT and +B2GPI IgG and is diagnosed with APS. She is started on a heparin drip and warfarin.

- What is her target INR?
- What if she had presented with a DVT instead of a CVA?
Controversies in anticoagulation intensity in APS

Rheum: High Dose Warfarin
- Small to medium sized retrospective studies
- High dose warfarin therapy superior to low dose therapy in preventing recurrent thromboses
- Retrospective analysis suspect: How do we know how close therapy was to target INR? Confounding? Bias?

Heme: Standard Dose Warfarin
- RCT showing no difference in risk of recurrent thrombosis with standard versus high dose warfarin

Rheum: Argument for High Dose Warfarin
- More than 10 fold reduction in events in people with INR >3 vs. INR <3

Heme: Standard Dose Warfarin
- RCT showing no difference in risk of recurrent thrombosis with standard versus high dose warfarin
Heme: Standard Dose Warfarin

- RCT of 114 patients followed for 2.7 years
- Frequent INR monitoring

Crowther et al., NEJM 2003;349(12):1133-1138

Moderate- vs. High-intensity Warfarin

High-intensity warfarin (target INR 3-4) was not superior to moderate-intensity warfarin (target INR 2-3)

Issues with Crowther Study

- Rules changed midway to extend enrollment (fewer thromboses than expected)
- Duration of follow-up reduced for final pt from 2 years to 6 months
- Excluded patients with history of recurrent events (lower risk group)
- Fewer patients with arterial events (recent CVA excluded)

Issues with Crowther Study

<table>
<thead>
<tr>
<th></th>
<th>Mod</th>
<th>High</th>
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<tbody>
<tr>
<td>Ave INR</td>
<td>2.3</td>
<td>3.3</td>
</tr>
<tr>
<td>Above</td>
<td>11</td>
<td>17</td>
</tr>
<tr>
<td>%Target</td>
<td>71</td>
<td>40</td>
</tr>
<tr>
<td>%Below</td>
<td>19</td>
<td>43</td>
</tr>
</tbody>
</table>

Most thromboses took place when INR was subtherapeutic
### APS Therapy: Secondary Prophylaxis

- **Secondary venous thrombosis prevention**
  - Initial therapy with unfractionated or low-molecular-weight heparin, followed by long-term anticoagulant therapy with a vitamin K antagonist such as warfarin (target INR 2-3)
  - Higher-intensity warfarin therapy (INR 3-4) did not further reduce the risk of recurrent thrombosis in RCTs

- **Secondary arterial thrombosis prevention**
  - Initial therapy with unfractionated or low-molecular-weight heparin, followed by long-term anticoagulant therapy with a vitamin K antagonist such as warfarin
  - Higher-intensity warfarin therapy (INR 3-4) preferred by some based on retrospective data and few patients with arterial thrombosis enrolled in RCTs
  - Aspirin monotherapy may be sufficient in older adults with stroke and low titer anticardiolipin antibodies

### Warfarin mechanism of action

- Interferes with vitamin K dependent carboxylation in the liver
- Inhibits levels of procoagulant factors II, VII, IX, and X and anticoagulant proteins C and S
- Paradoxical increase in coagulation with initiation of warfarin due to variable half lives of previously formed circulating clotting factors and anticoagulant proteins
  - Factor VII and protein C have short half-lives (6 hours)
  - Although depletion of factor VII leads to rise in INR, patient not protected from thrombosis until factor X (half life 40 hours) and factor II (half life 60-70 hours) levels fall substantially
- Bridging with UFH or LMWH should be administered with warfarin initiation until INR has been in therapeutic range for at least 48 hours

### Case 3: APS and family planning

- A 24-year-old woman with APS, manifested by a positive lupus anticoagulant test and brachial artery thrombosis, is maintained on warfarin and would like to discuss contraceptive options with you. She is currently using the barrier method only. She reports issues with menorrhagia.
Question

• What contraceptive method would you recommend for this patient?
  
  A. Copper IUD  
  B. Mirena IUD  
  C. Progestin-only OCP  
  D. Nuvaring

PEDS and contraception

• Estrogen-containing methods are contraindicated in patients with aPL+ (whether or not they have APS) due to risk of thrombosis
  
• Copper IUD is safe, but often not ideal as it can increase menstrual bleeding (especially in women on anticoagulation)
  
• Progestin-only OCP has high failure rate and is not ideal for patients on teratogens

Choosing a contraceptive method

• Decisions regarding any contraceptive method in patients with APS must take into account:
  
  - The risk of the method
  - The risk of unplanned pregnancy
  - The ease of use
  - The efficacy of the method

Long Acting Reversible Contraception

• Intrauterine device (IUD):
  
  - Primary mechanism of action: prevents fertilization and impairs implantation
  - Extremely low failure rate (similar to tubal ligation)
  - Safe for all SLE patients, including aPL positive patients
  - Levonorgestrel IUD (Mirena and Skyla): every 3-5+ years; reduction in menstrual bleeding and dysmenorrhea
  - Copper IUD: every 10 years; often increases menstrual bleeding so not ideal for women with heavy periods at baseline especially if on anticoagulation
  - No increased risk of infection in HIV+ patients (no data in SLE)

• Progestin implant (Nexplanon):
  
  - Every three years
  - Note: third-generation progestin may be more thrombogenic
Hormonal Contraceptives

- Estrogen-containing contraceptives
  - Combined estrogen-progestin pills (daily)
  - Vaginal ring (applied monthly)
  - Transdermal patch (applied weekly)
  - Increased risk of thrombosis (3-5X inc risk of VTE, 2X inc risk of CVA)
  - All are contraindicated in setting of very active lupus or presence of aPL or previous history of thrombotic event

- Progestin-only contraceptives
  - Progestin pill (“mini-pill,” daily): break-through bleeding, must take at same time every day, otherwise high failure rate
  - DMPA (“Depo-provera,” injection every 3 months): break-through bleeding, delayed return to fertility, decreased bone density due to inhibition of ovulation

Question

- What contraceptive method would you recommend for this patient?
  A. Copper IUD
  B. Mirena IUD
  C. Progestin-only OCP
  D. Nuvaring

Case

- A 24-year-old woman with APS, manifested by a positive lupus anticoagulant test and brachial artery thrombosis, is maintained on warfarin and planning to conceive.

Question

- In addition to stopping warfarin and starting low-dose aspirin, what other medication(s) would you recommend for this patient during pregnancy?
  A. Full-dose LMWH
  B. Full-dose LMWH and hydroxychloroquine
  C. Prophylactic-dose LMWH
  D. Prophylactic-dose LMWH and IVig
Management of APS During Pregnancy

- Discontinue warfarin due to teratogenicity prior to pregnancy when patient is trying to conceive or immediately upon becoming pregnant.
- Start another form of anticoagulation – dose depends on APS manifestation.

Management of Obstetric APS

- Combination of heparin and aspirin is superior to aspirin alone in enhancing live birth in obstetric APS.
- Patients who received heparin and ASA were 1.3 times more likely to result in live birth than patients who received ASA alone.
- Number needed to treat to result in 1 live birth = 5.6.
- Also reduces risk of preeclampsia.

In addition to stopping warfarin and starting low-dose aspirin, what other medication(s) would you recommend for this patient during pregnancy?

A. Full-dose LMWH
B. Full-dose LMWH and hydroxychloroquine
C. Prophylactic-dose LMWH
D. Prophylactic-dose LMWH and IV Ig
What about our other answer choices?

- **Prophylactic dose LMWH** would be appropriate if her APS manifestation were pregnancy morbidity.
- **Hydroxychloroquine**: some promising retrospective data, but no prospective data to support routine use in APS patients without SLE.
- **IVIg**: some reproductive immunologists advocate IVIg for women with +aPLs and prior pregnancy losses or infertility, but small RCTs have not shown improvements in outcomes.

Pregnancy complications associated with antiphospholipid antibodies

- Presence of aPL is a major risk factor for pregnancy loss and other adverse outcomes, especially in association with SLE.
- In the PROMISSE study, LAC was identified as the most important risk factor for adverse pregnancy outcomes in aPL-positive women (with or without SLE) – RR 12.
- ACL and B2GP1 were not independently associated with APO.

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**Case 4: APS and DOAC**

A 42-year-old woman with SLE presents to clinic for follow up. She was diagnosed with a new left lower extremity deep vein thrombosis in the Emergency Department 3 days ago and was started on rivaroxaban. Her past medical history is notable for an ischemic cerebrovascular accident last year for which she takes aspirin.

On examination today, her vital signs are stable. She has no calf tenderness but has obvious livedo reticularis of the upper and lower extremities.
Her laboratory testing from 4 months ago revealed the following:

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Results</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antinuclear antibodies</td>
<td>1:40</td>
<td>1:40 or less</td>
</tr>
<tr>
<td>Anticardiolipin antibodies</td>
<td>82 GPL</td>
<td>Less than 20 GPL</td>
</tr>
<tr>
<td></td>
<td>78 MPL</td>
<td>Less than 20 MPL</td>
</tr>
<tr>
<td>Beta2-glycoprotein antibodies</td>
<td>58 SGU</td>
<td>Less than 21 SGU</td>
</tr>
<tr>
<td></td>
<td>70 SMU</td>
<td>Less than 21 SMU</td>
</tr>
<tr>
<td>Lupus anticoagulant</td>
<td>Positive</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Question

What recommendation should you make about her anticoagulation regimen?

A. Continue rivaroxaban with no change
B. Switch from rivaroxaban to dabigatran
C. Switch from rivaroxaban to warfarin
D. Switch from rivaroxaban to enoxaparin and bridge to warfarin

Direct Oral Anticoagulants

Direct thrombin inhibitors
- Dabigatran

Direct factor Xa inhibitors
- Apixaban
- Edoxaban
- Rivaroxaban

Approved for primary treatment and prevention of VTE, prevention of stroke and systemic embolism in patients with non-valvular heart disease, and treatment of acute coronary syndromes

In the major clinical trials of DOACs versus warfarin in VTE, APS was not documented

Rivaroxaban vs. VKA for APS
3 year open label non-inferiority RCT

- Rivaroxaban did not show non-inferiority to VKA
- Stroke occurred more commonly in patients treated with rivaroxaban (RR 1.90 [95% CI, 1.12 to 3.21])
- Potentially increased risk for recurrent thrombosis in RVX-treated patients with previous arterial thrombosis, livedo racemosa, or APS-related cardiac valvular disease
- Confirmed concerns seen in other studies
What recommendation should you make about her anticoagulation regimen?

A. Continue rivaroxaban with no change  
B. Switch from rivaroxaban to dabigatran  
C. Switch from rivaroxaban to warfarin  
D. Switch from rivaroxaban to enoxaparin and bridge to warfarin

Case 5: Catastrophic APS

You are consulted to see a 32-year-old woman who is currently hospitalized after a recent delivery. She was hospitalized at 28 weeks of pregnancy with new-onset proteinuria (5.2 g/24 hr) and hypertension (maximum 172/101 mmHg) and was diagnosed by the obstetric team with preeclampsia and started on magnesium. Within 6 hours, she developed generalized seizures and was subsequently diagnosed with eclampsia, necessitating an emergency C-section delivery. Now, 3 days after delivery, her medical condition is worsening. A computed tomography scan of her abdomen shows a normal-sized spleen and liver with a 3-cm area of liver infarction. Her pulmonary status is unstable, currently requiring 6L of oxygen by nasal cannula.

• She has no systemic symptoms aside from typical pregnancy symptoms. She has no significant small joint pain, rashes, episodes of chest pain, alopecia, mouth ulcers, or fevers. She has had 3 prior pregnancies, including a loss at 13 weeks of gestation and a preterm delivery due to preeclampsia at 25 weeks 2 years ago. She has never had high blood pressure or protein in her urine except for during pregnancy.
Case, continued

- On physical examination, she is an uncomfortable woman who is tachypneic and anxious. She has been afebrile, and her blood pressure is now 142/82 mmHg. The HEENT examination is normal, and her joints are not inflamed. She has crackles in her lung bases. She has tachycardia, with a II/VI systolic ejection murmur. Her abdomen is tender, particularly in the right upper quadrant. Her fingers and toes have multiple splinter hemorrhages under the nailbeds that are tender to palpation and new since admission. In addition, she has a new confluent petechial rash over her shins. She is neurologically and cognitively intact.
- She has a positive antinuclear antibody (ANA) titer, reported as 1:640 (reference range: 1:40 or less), which leads to your consultation.

<table>
<thead>
<tr>
<th>Laboratory Test</th>
<th>Result: At Admission</th>
<th>Result: Current (3 days after admission)</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aminotransferase, serum alanine (ALT, SGPT)</td>
<td>66 U/L</td>
<td>950 U/L</td>
<td>10-40 U/L</td>
</tr>
<tr>
<td>Aminotransferase, serum aspartate (AST, SGOT)</td>
<td>82 U/L</td>
<td>1209 U/L</td>
<td>10-40 U/L</td>
</tr>
<tr>
<td>Bilirubin (total), serum</td>
<td>0.8 mg/dL</td>
<td>5 mg/dL</td>
<td>0.3-1 mg/dL</td>
</tr>
<tr>
<td>Creatinine, serum</td>
<td>0.7 mg/dL</td>
<td>4.2 mg/dL</td>
<td>0.7-1.5 mg/dL</td>
</tr>
<tr>
<td>Hemoglobin, blood</td>
<td>11 g/dL</td>
<td>9.5 g/dL</td>
<td>12-16 g/dL</td>
</tr>
<tr>
<td>Leukocyte count</td>
<td>5000/μL</td>
<td>6200/μL</td>
<td>4000-11,000/μL</td>
</tr>
<tr>
<td>Platelet count</td>
<td>130,000/μL</td>
<td>120,000/μL</td>
<td>150,000-450,000/μL</td>
</tr>
<tr>
<td>Urinalysis</td>
<td>4+ protein, 50+ white blood cells, 50+ red blood cells, and granular casts</td>
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</tbody>
</table>

Question

- Which test is most likely to clarify this patient’s diagnosis?
  A. ADAMTS13 (a disintegrin and metalloprotease with thrombospondin type 1 motif 13) activity
  B. Anticardiolipin and anti–beta-2 glycoprotein 1 antibodies
  C. Anti–double-stranded DNA antibody, anti-Smith antibody, complement levels
  D. Natural killer cell activity, ferritin level, and soluble CD25 level

Catastrophic Antiphospholipid Syndrome

- Multiple simultaneous or evolving thrombotic events involving microvasculature
- Clinical manifestations include:
  - Renal: severe HTN, AKI
  - Pulm: ARDS, DAH
  - Hemo: DIC, MAHA, thrombocytopenia
  - Neuro: Cerebral ischemia, stroke
  - Cutaneous: livedo reticularis, digital necrosis
  - Cardiac involvement: systolic dysfunction, MI, valvular lesions, atrial thrombus
- Can be presenting manifestation of APS
- Affects ~1% of patients with APS

Thrombotic Manifestations in CAPS

<table>
<thead>
<tr>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intestinal involvement</td>
</tr>
<tr>
<td>Brain</td>
</tr>
<tr>
<td>Thyroid</td>
</tr>
<tr>
<td>Cardiac</td>
</tr>
<tr>
<td>Pancreatic</td>
</tr>
<tr>
<td>Liver</td>
</tr>
<tr>
<td>Retinal involvement</td>
</tr>
<tr>
<td>Cohesions, other tissues</td>
</tr>
<tr>
<td>Renal</td>
</tr>
<tr>
<td>Common involvement</td>
</tr>
<tr>
<td>Nervous system</td>
</tr>
<tr>
<td>Peripheral arterial thrombosis</td>
</tr>
<tr>
<td>Bone marrow necrosis</td>
</tr>
</tbody>
</table>

CAPS classification criteria

1. >3 organ/tissue involvement
2. <1 week progression of disease
3. Histopathologic confirmation in 1 tissue
4. Lab confirmation aPL

- Definite (all 4)
- Probable (All 4 with 2 organs involved, 1/2/4, 1/3/4 within 1 month despite anticoagulation)

Precipitating Factors of CAPS

<table>
<thead>
<tr>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infections</td>
</tr>
<tr>
<td>Respiratory tract</td>
</tr>
<tr>
<td>Cutaneous</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Ocular</td>
</tr>
<tr>
<td>Surgery, stent, and invasive procedures</td>
</tr>
<tr>
<td>Neoplasia</td>
</tr>
<tr>
<td>Steroid withdrawal/low dose</td>
</tr>
<tr>
<td>Mechanic complications</td>
</tr>
<tr>
<td>Blood transfusion</td>
</tr>
<tr>
<td>Certain medications</td>
</tr>
<tr>
<td>No factor identified</td>
</tr>
</tbody>
</table>

CAPS – Prognosis

- Poor prognostic indicators
  - Older age
  - Number of involved organs
  - Splenic, cardiac, intestinal involvement

- Overall 50% mortality – but perhaps improving (30%) with better recognition and more aggressive therapy
What about our other answer choices?

- **ADAMTS13 testing is incorrect because this patient does not have TTP. Patients with TTP present with microangiopathic hemolytic anemia, documented with schistocytes on peripheral blood smear and severe thrombocytopenia (platelet count < 30,000/µL), which she lacks. In addition, she does not have the neurologic symptoms (headache, confusion, stroke-like manifestations), which are seen in two thirds of patients with TTP.**

- **Testing for anti–double-stranded DNA antibody, anti-Smith antibody, and complement levels is incorrect because this patient does not have a history consistent with systemic lupus. It is uncommon for women with lupus to only have disease activity or onset during pregnancy. When this happens, most women will have typical symptoms of a lupus flare, such as arthritis, rashes, ongoing fatigue, recurrent fevers, lymphadenopathy, etc., in addition to signs of nephritis. In addition, lupus flares typically evolve more slowly than CAPS.**

- **Testing for natural killer cell activity, ferritin level, and soluble CD25 level is not correct because this patient does not have features of hemophagocytic lymphohistiocytosis/macrophage activation syndrome (HLH/MAS). In HLH/MAS, natural killer cells and cytotoxic T cells fail to eliminate and control activated macrophages, leading to hemophagocytosis and organ dysfunction. This patient lacks many of the key clinical features of HLH/MAS, which include fevers, hepatosplenomegaly, dramatic cytopenias, and elevated ferritin and lactate dehydrogenase levels.**