A Case of Severe Hemolysis in CLL

Josh Veatch
75 man with CLL presents to a hospital in Wenatchee with fever several hours after rituximab infusion
Background of his CLL

- May 2013: Patient was diagnosed with CLL-WBC 25K, Rai stage I (adenopathy), CD38-, ZAP-70+

- December 2013: WBC 144K, hct 38, plt normal, started on oral chlorambucil

- Decision to start treatment based on rapid doubling, patient preference
• May 2014: hct 28, WBC 50-60K, DAT negative
• June 17, 2014: started weekly rituximab
  – First rituximab dose with hypersensitivity reaction, but subsequent doses tolerated well
• July 8, 2014: tolerated 4th dose of rituxan infusion, went home and had a fever later that day to 39C
Initial presentation

- Fever, hypotension, shortness of breath
- Hct 24
- CT chest with adenopathy, no infiltrates
- Blood cultures negative
History

• Past Medical History
  – CLL Rai 1
  – GERD
  – HTN
  – Prostatitis
  – Depression

• Allergies- NKDA

• Medications
  – Lexapro 10mg QD
  – Omeprazole 20mg QD

• Social History
  – Independent
  – East Wenatchee

• Family History
  – Mother with CLL in 90s
7/8: Admission blood cultures negative, treated with meropenem
7/10: LDH, haptoglobin wnl, retic 1.0%
7/12: acutely developed vasculitic rash
7/13: pulse dose solumedrol started
7/14: 1g/kg IVIG LDH 1800+
7/15: Transfer to UWMC

Total of 8U PRBCs, DAT+
Exam on presentation to UWMC

• T 36.2 P 110 R 16 BP 139/95 sat 95% RA

• Physical exam:
  – Jaundice
  – Shotty cervical adenopathy
  – Bilateral pulmonary rales
  – No splenomegaly
  – Multiple palpable 1-2cm purpuric plaques on legs
Exam
Labs on transfer to UWMC

- Na 135 K 5.3 Cl 107 HCO3 18 BUN 98 Cr 2.16
- AST 60 ALT 32 Alk Phos 28 Bilirubin 14 (8.4 direct)
- WBC 43K (96% lymphs) hct 12 MCV 101 Plt 104 RDW 26
- Retic 2% Haptoglobin 12 INR 2.2 LDH 597 PTT 30 Fibrinogen 690 Ferritin 75,000
- SPEP polyclonal
- Blood cultures 1/2 Clostridium Ramosum
Smear
Definitions

• Warm antibody
  – Anti RBC antibody that reacts best at 37C
• Cold antibody
  – Anti RBC antibody that reacts best below 37C
• Cold agglutinin
  – Antibody that causes RBC aggregation most effectively below 37C
• Cold agglutinin disease
  – Immune hemolytic anemia from cold antibodies
Cold agglutinin disease

- Many cold antibodies are not clinically significant
- Generally IgM (warm antibodies are generally IgG)
- Often a chronic, low grade disease
- Thermal amplitude, temperature of reactivity can dictate clinical severity
- Responds poorly to immune suppression
Direct Antiglobulin Test (Coombs test)

• Polyspecific 3+
• anti-IgG negative
• Anti-C3 3+

• Cold autoagglutinin anti-I

• Thermal amplitude
  – Reactive at 37C, 30C and 22C
Bone marrow

- 50-80% small lymphocytes, no evidence of transformation
- Relative erythroid hyperplasia, some megaloblastoid changes
- No evidence of hemophagocytosis
Cold agglutinin disease

http://faculty.madisoncollege.edu/mljensen/BloodBank/lectures/complement.htm
The I/i antigen system

Blood Group Antigen Gene Mutation Database
Autoimmune hemolytic anemia in CLL

- 4.3% in one series of 1203 CLL patients, 1/3 at presentation
- 87% IgG, 13% IgM
- Correlated with male gender, age, elevated lymphocyte count
- All IgM cases (7) were anti-I and reactive at 37C

_Blood._ 2000 May 1;95(9):2786-92.
Hemolysis and survival in CLL

Blood. 2000 May 1;95(9):2786-92.
Infection and cold agglutinin disease

• Mycoplasma
  – Anti-I
  – Rarely can have severe hemolysis
  – Usually 1-2 weeks after febrile illness

• EBV
  – Anti-i, usually mild

• Others
  – Adenovirus, chlamydia, influenza, varicella, listeria
Drugs causing/exacerbating hemolysis

- Fludarabine
- Cladribine
- Chlorambucil
- Mechanism not clear, but the resultant antibodies do not require drug for RBC binding (not a haptan mechanism)
• Cold agglutinin: antibody that agglutinates red cells better at colder temperatures

• Cryoglobulinemia: monoclonal or polyclonal antibodies that form protein complexes that precipitate at colder temperatures
“warm” agglutinin hemolysis

• IgM agglutinin that is reactive at 37C
• Rare entity
  – Red Cross in southern California had 49 cases in 25 years
• 11/49 cases of hemolysis were fatal, higher fatality rate in older patients

Transfusion. 2009 Feb;49(2):235-42
Treatment of cold agglutinin disease

• Steroids
  – At best 14% response rate from multiple series

• Rituximab
  – Response rates 45-58%, remission duration median 11 months

• Alkylators, purine analogs

• Limited benefit in the acute setting

*Blood.* 2013 Aug 15;122(7):1114-21
Treatment of cold agglutinin disease

• Blood warming

• Plasmapheresis
  – IgM is entirely intravascular, so can be removed more efficiently
  – Can exchange with albumin or with plasma
Effect of eculizumab in a patient with cold agglutinin disease.

Improvement of hematocrit with plasma exchange

- 21U PRBCs were given
- Plasmapheresis 7/15, 7/17, 7/19, 7/21, 7/22
An unfortunate complication

- On HD#2 at UWMC, the patient developed rapid atrial fibrillation and chest pain with NSTEMI during attempted plasma exchange
- Acute CHF leading to anuric renal failure and acute liver failure, respiratory failure requiring intubation
- The patient moved to comfort care and passed away on HD#8
Summary

• 75M with active CLL being treated with rituximab
• Presentation with fever with subsequent development of vasculitic rash and fulminant “warm” IgM anti-I hemolytic anemia
• Improvement of hemolysis with plasmapheresis
• MI related to anemia, subsequent multiorgan failure
Questions

• What was the trigger?
  – Infection?
  – Rituximab? Serum sickness?

• Why were there so few reticulocytes?
  – CLL vs. kinetics
Variability of the Erythropoietic Response in Autoimmune Hemolytic Anemia: Analysis of 109 Cases

By Jane L. Liesveld, Jacob M. Rowe, and Marshall A. Lichtman

37% of patients with autoimmune hemolytic anemia had reticulocyte production indices less than 2.0

- About half of these increased with time

- 54% had marrows, 75% of those showed erythroid hyperplasia

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