4-29-2020

Autoimmune Hemolytic Anemia In Chronic Lymphocytic Leukemia

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Introduction

Patients with chronic lymphocytic leukemia have a 5-10% risk of developing autoimmune complications, the most common of which is autoimmune hemolytic anemia. Here we present a case of AIHA in a patient with suspected CLL that underscores several of the diagnostic and treatment challenges unique to this process.

Case Presentation

History of Present Illness

- 79 year old man with progressive dyspnea, exertional chest pressure x 3 weeks; worse over the past few days
- Has chronic stable pedal edema
- No PND, orthopnea, palpitations, syncope
- Went to PCP noted to be jaundiced with mild confusion; sent to ED for ACS rule out and further workup

Past Medical History

- Persistent leukocytosis with flow cytometry suspicious for CLL but no formal diagnosis
- Paroxysmal atrial fibrillation
- Hypertension
- Hypothyroidism
- Type 2 Diabetes Mellitus
- Gout

Physical Exam

- VS: HR 74 RR 16 Temp 36.8 BP 107/51 O2 100% RA
- Gen: Elderly man in no acute distress, mildly jaundiced
- Pulm: No increased WOB, CTAB
- Cardio: RRR w/ 2/6 systolic murmur best heard at the LUSB. No JVD
- Abd: Active bowel sounds, non-tender, splenomegaly
- Bilateral pedal edema with venous stasis changes
- Neuro: Intermittently confused but oriented x4. CN2-12 intact. No focal findings

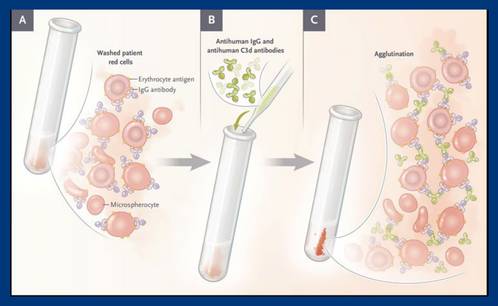
Labs and Imaging

- Leukocytosis with WBC 20.8, 80% lymphocytes, 3% atypical lymphocytes
- Severe anemia with Hgb 5.1, MCV 115. Normal platelets.
- Total bilirubin 4.1, normal LFTs
- Haptoglobin < 30, LDH 235, DAT +complement/IgG, retic count 7.3%
- Negative troponin, BNP 172, EKG NSR with no significant changes
- CTA negative for PE
- CT abd/pelvis with cholelithiasis and splenomegaly

Hospital Course

- Given 95 mg of prednisone in the ED. PRBC ordered
- Lab was unable to find compatible blood; was given 3 units ABO and RhD compatible blood over 4 hours with premedication and careful monitoring for transfusion reaction
- Hbg responded appropriately to transfusion
- Started on 80 mg Prednisone daily
- LDH, reticulocyte count, Tbili downtrended
- Hgb remained stable
- 1 episode of recurrent chest discomfort while straining to have a bowel moment but otherwise asymptomatic for remainder of hospital course
- Discharged on 80 mg qd prednisone with outpatient oncology follow up

Coombs Testing



Red Cells in the Spleen

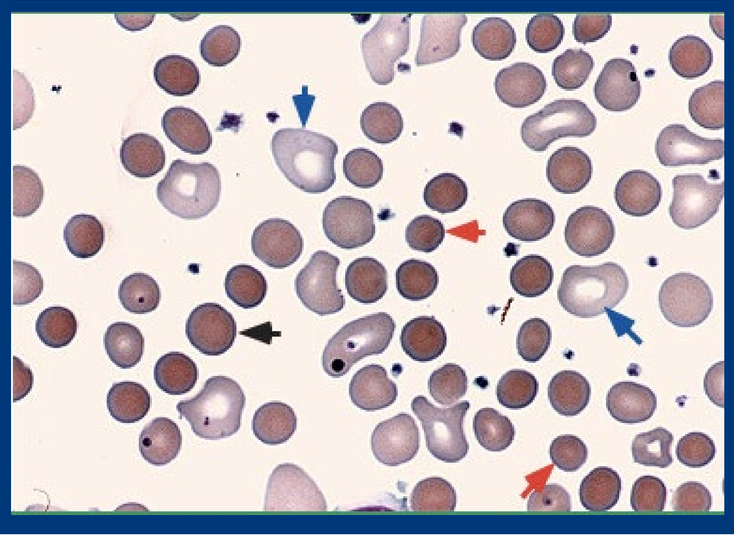
Baseline characteristics of 60 patients with AIHA

Mean age at AIHA onset	53.6 ± 22.8 years (mean ± SD)
Percent females	50%
Clinical symptoms at onset	87%
Anemia-related symptoms	75%
Jaundice/dark urine	33%
Chest pain/coronary syndrome	7%
Venous thrombosis	20%
Mean hemoglobin at onset	6.4 ± 1.7 g/dL
Mean reticulocytes at onset	285 ± 175 x 103/microL
MCV at onset	108 ± 14 fL
Decreased haptoglobin	93%
Increased LDH	93%
Increased bilirubin	82%
Spherocytes at onset	41%
Direct antiglobulin test positivity	100%
Secondary cause present	62%
Lymphoproliferative disorder	33%
Autoimmune disorder	14%
Miscellaneous disorders	14%
	(UC, immunodeficiency, HCV, CA, drug)

Common causes of hemolysis in adults

Extravascular destruction of red blood cells
Intrinsic red blood cell defects
Enzyme deficiencies (eg, G6PD, pyruvate kinase)
Hemoglobinopathies (eg, sickle cell disease, thalassemias)
Membrane defects (eg, hereditary spherocytosis)
Extrinsic red blood cell defects
Liver disease
Hypersplenism
Infections (eg, *Bartonella*, *Babesia*, malaria)
Oxidant agents (eg, dapsone, nitrites, aniline dyes)
Other agents (eg, lead, copper, snake and spider bites)
Autoimmune hemolytic anemia (warm- or cold-reacting, drugs)
Intravenous immune globulin infusion
Intravascular destruction of red blood cells
Microangiopathic hemolytic anemia (eg, TTP, HUS, aortic stenosis, prosthetic valve leak)
Transfusion reactions (eg, ABO incompatibility)
Infection (eg, clostridial sepsis, severe malaria)
Paroxysmal nocturnal hemoglobinuria
Following intravenous infusion of Rho(D) immune globulin
Following intravenous infusion with hypotonic solutions
Snake bites
Exposure to compounds with high oxidant potential (eg, copper poisoning, Wilson disease)

Autoimmune hemolytic anemia on peripheral smear



Peripheral blood smear from a patient with AIHA due to a warm-reactive immunoglobulin G (IgG) antibody. Highlighted are dark red, small microspherocytes (red arrows) and larger spherocytes (black arrow) (x1000). Many large, irregular, blue-tinted red cells are also present, representing reticulocytes (blue arrows).

Case Presentation

Outpatient Course

- Now following with oncology
- Flow cytometry and FISH analysis confirmed CLL diagnosis; monotypic B-cell population
- FISH positive for deletion of 13q14 with no other abnormalities
- This is the most common deletion in CLL (reported in 10-20% of cases with conventional cytogenetics and 64% by FISH analysis)
- When present as sole abnormality this deletion is associated with a good prognosis with median survival longer than for CLL patients with normal karyotype
- Started on Ibrutinib
- Will continue prednisone until Hgb >10, then began slow taper over course of 4-6 months
- PJP prophylaxis with Bactrim while on high dose steroids; also Folic acid, Protonix

Key Points

In virtually all cases of warm AIHA cross-matches will be incompatible

- Auto-antibodies will recognize blood group antigens and react to the vast majority of donor red cells. Consequently, ABO and RhD matched blood should be given in severe anemia requiring urgent blood transfusion.

- The blood should be given slowly with careful monitoring for transfusion reaction, though the risk of this is low (approaching zero without previous sensitization to foreign antigens; less than 10% with previous transfusion or pregnancy

There is a substantial risk of VTE in patients with AIHA, 15-30%

- It is important to evaluate for concomitant PE in patients presenting with AIHA, especially as these patients also frequently present with dyspnea, hypoxia and tachycardia

AIHA is often a chronic, relapsing condition.

- Steroid courses of at least 6 months as well as the addition of Rituximab can decrease recurrences of AIHA

Lymphoproliferative disorders, and specifically CLL, are the most common cause of secondary warm AIHA.

- Given relatively high rate of AIHA in CLL workup for hematologic malignancy should be considered in patients presenting with apparently idiopathic AIHA.

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