Auto-Immune Hemolytic Anemia

James J. Stark, MD, FACP
Medical Director, Cancer Program and Palliative Care
Maryview Medical Center

Professor of Medicine, EVMS
Case Number 1

- AT: 67 y.o. man with auto-immune hemolytic anemia
- Presented in 1965 with initial episode of AIHA treated successfully with short course of steroids
Case, Continued

- In adulthood developed NIDDM, CAD and hypercholesterolemia; s/p coronary bypass and stent placement
- Prior to referral was found to be newly and severely anemic:
  - Hematocrit 24%, MCV 115, Retics 12.7%
  - Bilirubin 1.4 all indirect
  - WBC 6,700 78% PMN, platelets 136,000
  - Normal B12, folate and ferritin
- Peripheral blood smear…
Case, continued

- Anti-globulin test positive for anti-IgG
- Anti-C-3 was negative
- Therefore diagnosed with so-called warm-reacting IgG AIHA.
- No symptoms to suggest underlying cause such as lupus or lymphoma
- On no drug associated with AIHA
- Underwent further evaluation:
  - ANA negative
  - CT C/A (ins. co refused to allow pelvis (!!))…
CT of Chest

CAPP
C: GASTROVIEW
Se: 2/2
Im: 22/2
Ax: I81.3 (COI)

1940 May 19 M 241603801
Acc: 5362188
2008 Mar 19
Acq Tm: 20:13:15

512 x 512
STANDARD

120.0 kV
344.0 mA
5.0 mm.
Tilt: -0.5
ET: 1.1 s
GP: 0.7 s
TS: 13.75 mm/s
CT Chest, cont.

CAPP 1940 May 19 M 241603801
C: GASTROVIEW Acc: 5362183
Se: 2/2 2008 Mar 19
Im: 17/2 Acq Tm: 20:13:15
Ax: 156.3 (COI)

120.0 kV
425.0 mA
5.0 mm
Tilt: -0.5
ET: 1.1 s
GP: 0.7 s
TS: 13.75 mm/s
SPR:
Lin: DCM / Lin: DCM / Id JD
W: 400 L: 40

DFOV: 44.0 x 44.0 cm
Lung Windows
Case Management

• With diagnosis in hand, without underlying disease definable, started on Prednisone at 60 mg/day; diabetes immediately went out of control necessitating addition of insulin
• Rapid decrease in retics and rise in hematocrit
• When tapering of Prednisone attempted retics remained somewhat elevated and hematocrit stayed in 20’s as dose of Prednisone was reduced to 20 mg/day
• What to do next....
Options for Management

• Keep on Prednisone indefinitely – unpalatable given array of side effects:
  – Diabetes
  – Accelerated bone mineral loss
  – Altered host resistance
  – Cataract formation
  – Propensity to cause upper GI bleeding
• Take his spleen out
• Add a second drug…which drug?
Management, continued

• Choices of drug:
  – Immunosuppressant
    • Cyclosporine
    • Cyclophosphamide
    • Azothioprine
  – Anabolic Steroid
    • Danazol
  – Anti-B-cell monoclonal antibody (Rituximab)
Management, continued

• While being maintained on Prednisone at 20 mg/day, he received four doses of Rituximab at 375 mg/m²
• While awaiting a response he became acutely ill with fever and shortness of breath and was admitted to the hospital with bilateral pulmonary infiltrates
• X-rays…
Chest X-ray upon admission
Management, continued

- He remained gravely ill with pulmonary infiltrates which did not improve, and so underwent open-lung biopsy
- Pathology....
Subsequent Course

• Remained on high-dose steroids for pulmonary process, underwent tracheostomy for long-term ventilatory support and now, two months later, is getting slightly better
Case #2

- 54 y.o. man followed for three years for typical CLL
- WBC on presentation about 30,000; slowly climbed over the next three years to 50,000
- No anemia, thrombocytopenia; minimal adenopathy; no splenomegaly or constitutional symptoms
- No therapy offered ("pre-treatment phase")
Case #2, continued

• Presented 10 days ago with sudden drop in hematocrit from 44 to 24, brisk reticulocytosis (15%)
• WBC now 98,000 almost all lymphs; platelets still normal
• Peripheral blood smear…
Case #2, continued

- Presented 10 days ago with sudden drop in hematocrit from 44 to 24, brisk reticulocytosis (15%)
- WBC now 98,000 almost all lymphs; platelets still normal
- Peripheral blood smear…
- Nodes slightly bigger
- Spleen now palpable
- Coombs test:
  - 4+ positive for IgG and C3 coating his red cells
- Prednisone initiated; chemotherapy with Rituxan and Cytoxan just started
Case #2, continued

- On third day of chemotherapy his WBC is up to 206,000
- H/H = 5.6/17
- Retics 34%

- If no improvement by next week will recommend he undergo immediate splenectomy
Case #2 Therapy, continued

- Conventional first-line therapy for aggressive CLL usually includes Fludarabine
- Several well-documented reports of this drug causing AIHA in CLL patients where none previously existed…
- Therefore reluctance to use this agent
- Why should this be so?
Theoretical Basis for Fludarabine Effect

- Loss of cell tolerance
  - Fludarabine
  - T-cell

- Remnant B-cell
  - Autoantibody production

- Neoplastic B-cell
  - Antigen Presenting Cell

AUTOIMMUNE DISORDER
Case #2, continued

• Hence decision made to withhold Fludarabine for the moment
• Ultimate wisdom of this move to be determined
• Decision made on anecdotal evidence
Background: Terminology

• “Warm-reacting AIHA”
  – Abnormal IgG produced which reacts with proteins on red cell surface at body temperature (i.e., “warm”)
  – Associated with lupus and B-cell neoplasms (CLL, non-Hodgkin Lymphoma); can be triggered when CLL treated with anti-metabolites as discussed above
IgG-Associated AIHA: Laboratory Features

- Macrocytic anemia (reticulocytes are larger than mature RBC’s)
- Reticulocytosis
- ↑ LDH
- Very low or absent haptoglobin
- Occasional thrombocytopenia (Evans-Duane syndrome)
- Positive Coombs (anti-globulin) test
Positive Coombs Test

• Can be against IgG, C3 or both
• Intensity of positivity correlates with degree of hemolysis
• Can be produced by variety of drugs (classically penicillin) with or without associated hemolysis
  – Not the case with either of our patients
Clinical Findings in AIHA

• Anemia – can be severe enough to cause symptoms, as seen in our patients
  – Pre-existing heart or lung disease can dramatically effect impact of anemia

• Development of lymphoproliferative illness
  – Can occur after onset of AIHA; chicken and egg problem

• Hypercoagulability with venous thromboembolic disease
  – Associated with Anti-Phospholipid Syndrome

• Typically steroid responsive
Cold-Agglutinin Disease

• The other main type of AIHA
• Antibodies are usually IgM, anti-I in specificity
• Red cells agglutinate at room temperature, hence the term “cold agglutinins”
• Symptoms are those of anemia or of cryopathic phenomena
  – Acrocyanosis in the cold
• Typically steroid resistant
Acrocyanosis
Cold Agglutinins, continued

- Span the spectrum from benign to malignant disease
  - Chronic cold agglutinins unassociated with B-cell neoplasm; hemolysis usually mild, no other symptoms
  - Caused by benign monoclonal IgM-κ
  - Can transform into aggressive B-cell neoplasm with monoclonal IgM production
  - Can be associated with Mycoplasma pneumoniae or Epstein-Barr virus infections; at times can cause brisk hemolysis; self-limited
Differential Diagnosis of Cold Agglutinins

- Paroxysmal Cold Hemoglobinuria
  - IgG, after viral infection
- Drug-induced AIHA; pathologic IgM present but no cryopathic phenomena
- Essential cryoglobulinemia; cryopathic phenomena without classic cold agglutinin protein; often mixed IgG/IgM complexes
  - Often results in hyperviscosity and cutaneous vasculitis
  - Can be associated with B-cell malignancy in which case distinction from cold agglutinin can get murky
  - Ddx that of other cutaneous vasculitis syndromes
Treatment of Cold Agglutinin AIHA

- Steroids, splenectomy of no value
- Avoidance of cold, wearing gloves in cold weather
- Rituximab of value with or without interferon
- Plasmapheresis in emergent situations
- Chronic immunosuppression with cytotoxic agents
- Treatment in general less satisfactory than for warm AIHA
Back to Our First Patient

- What caused him to develop life-threatening pulmonary toxicity?
  - B-cell depletion with Rituximab not usually associated with opportunistic infections
  - Rituximab-induced acute pulmonary toxicity very rare (<20 cases reported); steroids allegedly of benefit; not clearly so in our case
- If he recovers the problem of what to do next remains
- Hemolysis gone ?from Rituxan or prolonged high-dose steroids used to treat lung process
- ??Underlying lymphoproliferative illness remains
- Arguably immaterial to recent therapy
Back to Our Second Patient

- AIHA *should* remit with control of his underlying malignancy
- May herald reactivity of disease
- What triggered this sudden untoward event is totally unknown
Conclusion

• AIHA is a rare but serious and potentially life-threatening condition if not cured with a short course of steroids

• Complex clinical picture; confusion with other conditions possible to the uninitiated
For a copy of this talk…

- Visit us on the web (www.StarkOncology.com) or at the office…