Marginal Zone Lymphoma Complicated by Refractory Anemia

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49 year-old female with JRA, normocytic anemia, and marginal zone lymphoma presents for evaluation for allogeneic SCT

- Anemia initially treated with erythropoietin
- Diagnosed with marginal zone lymphoma
- Attempted RCVP
- Red cells never recovered; diagnosed with MDS
- Failed erythropoietin; requiring 2-4 units of pRBCs weekly since 2009
- Iron overload with ferritin up to >20K, on chelation
The Patient

Review of Systems

- No f/c/ns, weight stable
- Intermittant knee and wrist pain
- No neurological symptoms
- DOE, fatigue, no CP or LE edema
- GERD, early satiety, bloating, nausea, no diarrhea or constipation

Physical Exam

T 97.5, P 116, RR 22, BP 108/64, SpO2 89%
- General: thin female, NAD
- HEENT: three 3-8mm oral ulcers
- No cervical, supraclavicular, axillary, or inguinal LAD
- Lungs: inspiratory wheeze, no crackles
- Heart: RRR, no murmur, no JVD, no edema
- Abd: mild tenderness in epigastrium, HSM, no ascites
- Extremities: no joint swelling, WWP
- Neuro: A&Ox4, CN2-12 intact, normal strength/sensation, normal gait
The Patient: Pre-transplant Labs

Peripheral smear: normocytic anemia, spherocytes, rouleaux, leukopenia
Flow 48% oligoclonal CD8+ T cells

MCV 87
ANC 1000
Retic 0.1%
Ferritin 11,000
% sat 118
LDH 168
Epo 3196
HFE H63D heterozygous

CRP 145
ANA, complements, RF: normal
αDSDNA elevated at 22
Total protein 10.5, albumin 2.7
IgG kappa 0.5 g/dL
Bence Jones 1g/24hr
INR 1.3, PTT 80, strong lupus inhibitor

HIV, HBV, HCV, Parvo, EBV, CMV PCRs all negative
The Patient: Peripheral Smear

Large Granular Lymphocytes
The Patient: Pre-transplant Marrow

Pronormoblast, but few other erythroid precursors

Normal Marrow with normal erythroid differentiation
The Patient: Pre-transplant Marrow

95% cellularity

Grade 2 reticulin fibrosis

Variable sized megakaryocytes

CD8+ T cells
The Patient: Pre-transplant Evaluation

- PFTs: SpO2 88%, pO2 58, CO 2.5%, FEV1 51%, FVC 47%, TLC 60%, DLCO 35%
- Echo: Mild pulmonary hypertension, EF > 60%, R atrial clot
- CT Chest, Abdomen, Pelvis:
The Patient: Pre-transplant Evaluation
The Patient

12/2012

03/2014
The Patient: Pre-transplant Evaluation
The Patient: Pre-transplant Evaluation

Lung Biopsy

CD138+ Plasma cells

CD20+ B cells
The Patient

• 2003: Fatigue and DOE; found to have anemia, treated with iron
• 2004: diagnosed with ET; treated with anagrelide and aspirin
• 2005: worsening anemia; treated with erythropoietin
• 2006: stopped anagrelide and aspirin. methotrexate for RA
• 2007: continued on erythropoietin
• 2008: cough and DOE; marginal zone lymphoma, treated RCVP. Epo stopped
The Patient

- Jan 2009: 95% cellularity, increased erythroid precursors, polyclonal CD8+ Tcell population 20%
- July 2009: neutropenia with antigranulocyte antibodies; Treated with low dose cyclosporine. Neutropenia resolved
- 2010: repeat lung biopsy with nonclonal plasma cell population. Spleen 14cm, started iron chelation with desferasirox
- 2011: 99% cellularity with dysplasia and fibrosis. <2% blasts. Chronic lymphoproliferative process. JAK2 negative
- 2012: added desferoxamine to desferasirox
The Patient

- September 2013: 90-95% cellularity. Normal myeloid differentiation, marked hypoplasia of erythroid maturation with L shift, M:E 10:1. atypical megakaryocytes, grade 2-3 fibrosis. <2% blasts. 5% plasma cells. No monoclonal B cells. Marked reversal CD4:8 ratio. Small population of lymphocytes with low CD5. 30% gamma-delta T cells, 30% CD57+ cells, no Tcell malignancy, 46XX, normal FISH and karyotype, normal “gene trails”

- Treated for 5 months with cyclosporine, continued on iron chelation
The Patient

- Pure red cell aplasia (1-2% pronormoblasts, rare erythroid precursors)
- Oligoclonal large granular lymphocyte population/LGL Leukemia
  - CD3+, CD8+, CD5 dim, CD7 dim Tcells (20-30% of marrow, 48% of peripheral blood); subset CD57+
  - CD4, CD1a, CD25, CD30, CD56 neg
- Evidence for autoimmune myelofibrosis and Felty’s syndrome vs Primary myelofibrosis
  - HSM
  - 95% cellularity, grade 2 fibrosis
  - Megakaryocytic hyperplasia with variable size and mild atypia
  - History of RA and low grade B cell lymphoma
- Hypergammaglobulinemia with polytypic plasmacytosis
- Marginal zone lymphoma with presumed plasmacytic differentiation
Pure Red Cell Aplasia

- **Diagnosis:**
  - Normochromic, normocytic anemia
  - Abs Retic <10K/μL
  - Normal WBC and Plt
  - Normocellular marrow with normal maturation of myeloid, lymphoid and megakaryocyte lineages, but few erythroid precursors

- **Etiology:** (60% antibody-mediated; 40% T-cell mediated)
  - LGL Leukemia
  - MDS
  - Thymoma
  - Virus (Parvo, HIV, HAV, HCV, EBV, CMV)
  - Lymphoproliferative disorders (CLL, HL, NHL, myeloma)
  - Drugs (erythropoietin)
Pure Red Cell Aplasia

- Treatment:
  - Cyclophosphamide (50-100mg daily vs 1g/m² Q3 weeks) and steroids
  - Cyclosporine (3-12mg/kg/day; goal trough 200) and steroids
  - Methotrexate (10mg/m² weekly)
  - High dose steroids (1mg/kg x 30 days then taper; or 60mg daily)
  - Rituximab
  - Alemtuzumab
  - ATG (15mg/kg/day x 10 days)

- Most important is to continue therapy for at least 3-4 months
Large Granular Lymphocytosis

- Large lymphocytes with abundant cytoplasm and azurophilic granules
- Cytopenia, splenomegaly, lymphocytosis, and autoimmune disease
- Treatment indications: ANC<500, recurrent infections, symptomatic anemia, active autoimmune disease
- Treatment (Cyclophosphamide, MTX, Cyclosporine, Alemtuzumab)
Marginal Zone Lymphoma

- Three unrelated subtypes: Nodal, extra-nodal, splenic
- Post-GC memory B cells under chronic immune stimulation
  - Autoimmune disease
  - Infection (Chlamydophilia, Lyme, Hpylori, Campylobacter)
- Stomach most common site (bowel, breast, head & neck, skin, lung)
- 30% associated with M-spike and plasmacytic differentiation
- Early stage disease usually treated locally (surgery or radiation)
- Stage III/IV disease is treated per FL algorithms (BR, RCHOP, RCVP; FR, lenolidomide + rituximab)
- Can transform to aggressive large cell lymphoma (DLBCL algorithms)
The Patient

- Polyclonal CD8+ T-cell population and paraproteinemia with substantial plasma cells
  - Methotrexate, however likely before development of PRCA
  - Cyclosporine, however possibly inadequate dosing
  - Rituximab

- How would you treat?
  - Treat lymphoma at same time?
  - Cover plasma cells upfront?
  - Do the CD8+ T-cells matter?
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References