Hairy Cell Leukemia: A Review of Underlying Biology and Treatment

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First, a Clinical Vignette...

TE is a 60M from Kodiak, Alaska.

HPI: Presented to PMD with **night sweats, early satiety, LUQ pain**. No fevers, infections, or bleeding/bruising. PMH otherwise unremarkable

**PE**: VS normal. Well-appearing. **Palpable splenomegaly 25 cm below L costal margin**. No LAD, hepatomegaly, skin changes.

**LABS**: WBC 3.3, ANC 2, Hct 41%, plts 69K

**CT Abdomen**: 36cm spleen. No lymphadenopathy.

**Peripheral Blood Flow Cytometry**: 42% population of cells with abnormal expression of CD11c, CD25 (low), CD20(bright), CD19 (bright), CD103, CD5 (low to absent), and normal expression of CD45 and CD38 without CD10.
HAIRY CELL LEUKEMIA OUTLINE

- Basics and Epidemiology
- History
- Morphology and Pathogenesis
- Clinical characteristics
- Diagnostic workup
- Therapeutic options
Hairy Cell Leukemia

• Rare Indolent B cell neoplasm
  – 2% of all leukemias
  – 600 new cases in US/yr
  – Splenomegaly, cytopenias, marrow fibrosis
  – “Hairy cells” found in blood and marrow
    Positive for CD19, CD20, CD22
    Neg for CD5, CD10, CD23
    Strong CD11c, FMC7, CD25, CD103
History of Hairy Cell Leukemia

• First reported by Ewald, 1923
  RE cells in blood
  “Leukemic Reticuloendotheliosis”
  Was actually describing an AML case

• Bouroncle et al, 1958
  26 case series
  Distinct clinical and pathologic features

• Schrek & Donelly, 1966
  Hairy cells in blood
  Flagellated cells in LN and spleen
  → “Hairy Cell Leukemia”
Hairy Cell Morphology

- Microvilli
- “Fluffy”
- Light basophilic cytoplasm
- Spongy chromatin
- Folded or oval nucleus
- Inconspicuous nucleoli
Hairy Cells: Diagnostic Assays

• TRAP stain
• Flow Cytometry
  Positive for CD19, CD20, CD22
  Neg for CD5, CD10, CD23
  Strong CD11c, FMC7, CD25, CD103
• IHC
  Annexin A1 +
  High cyclin D1
• Clonal Cytogenetic Abnormalities
  40% chr 5. Also Chr 7 or 14.
  Translocations uncommon
• Molecular Studies
  Ig heavy chain rearrangement
What is the Cell Origin of HCL?

• HCL: Late clonal B cells
  – No discrete B cell development stage
  – Mutated VH genes
  – Post-germinal center B cell
  – Related most to memory cells on gene expression array

• Etiology unclear
  – Environmental exposures:
    Pesticides/Fuel/Agent orange?

Why Are Hairy Cells Hairy?

- Microfilamentous cell surface projections
- Upregulation of actin and pp52 (Miyoshi et al, Leuk Res 2001)
- Reversible with IFNα
- Growth pathways linked with morphology

Tiacci et al, Nat Rev Cancer 2006
How HCs Survive: Evasion of Apoptosis
Where HCs Go: Adhesion and Homing Properties

Dissemination occurs within blood-related compartments.

Dissemination out of blood-related compartments is usually blocked.

- CXCR5
- CCR7
- CD62L

Homing to the splenic red pulp
- Homing to bone marrow and splenic stroma
- Vitronectin
- α₅β₁
- Hairy cell
- VCAM1
- Sinusoidal cell
- Homing to sinusoids in liver, spleen and bone marrow

Stromal cell

Peripheral blood
- Annexin-1
- Trans-endothelial migration
- Homing to lymph nodes
- Lymph node involvement
- Extra-nodal dissemination

MMP activity
- Degradation of pericellular matrix
- Extravasation
- Crossing tissue barriers
Hairy Cell Leukemia Pathophysiology

- Cytopenias
- Bone marrow fibrosis
- Splenomegaly
- Lack of lymph node involvement
- Other organ involvement
- Interaction with other immune cells
HCL Pathophysiology: Cytopenias

- Marrow infiltration
- Marrow fibrosis
  - Lack of LEB picture
- Hematopoietic suppression
  - Cytokines
- Splenomegaly

Marrow mononuclear infiltrate:
“Fried egg” appearance
Voluminous cytoplasm
HCL Pathophysiology: Bone Marrow Fibrosis

- Autocrine/paracrine
- FGF2
- IL-3R and FLT3 overexpression
- Fibronectin synthesis by HCL
- Interaction with stromal hyaluronan
- Fine reticulin fibers
- “Dry tap”
HCL Pathophysiology: Splenomegaly

**SPLEEN**

- White pulp obliterated
- Red pulp replaced with HCs
- Vascular channels and anemia
  - “pseudosinuses” and “red cell pooling” (aka “blood lakes”) via adhesion molecules
- Invasion and homing defects
  - splenic vitronectin and other chemoattractants
- Lack of fibrosis
  - no hyaluronan in spleen

[Image: ASH Image Bank]
HCL Pathophysiology

LIVER

- HC infiltration in portal tracts
- Minor sinusoidal involvement
- Marked reticulin fibrosis
- Main architecture preserved
- No clinical hepatomegaly or abnormal LFTs
HCL Pathophysiology

LYMPH NODES

- Not typically involved
- LNs lack L-selectin
- HCs lack CCR7
- Abdominal LNs can be involved in late disease

FNA of lymph node in HCL

Meara et al, Cytojournal 2006
HCL Cytokines:

- TNFα, GM-CSF: cell survival
- M-CSF: chemotaxis
- FGF: fibronectin production
- TGFβ: bone marrow suppression and fibrosis
Other HCL Cytokine Effects on Blood Cells

- Pancytopenia
- Monocytopenia
- T Cell Abnormalities
  - Reversed CD4:CD8 ratio
  - Skewed T cell repertoire
  - Clonally expanded T cells not HC-specific
  - Increased incidence LGL leukemia
HCL and Autoimmunity

• Seen in many NHLs
• Often improves/resolves with HCL treatment
• Vasculitis most common
• Others
  – Hemolytic anemias (WAIHA, CAIHA)
  – ITP
  – Evan’s Syndrome
  – IgA nephropathy
  – Demyelinating neuropathy
Epidemiology and Etiology

• 2% of all leukemias
  – 400 to 600 new cases in US/yr
HCL Clinical Presentation

• Presentation
  – Male:Female 4:1
  – White:Non-White 3:1
  – Median age 52

• Symptoms:
  – Abdominal fullness: 25%
  – Systemic complaints: 25%
  – Bruising/bleeding or recurrent infection: 25%
  – Asymptomatic: 25%

• Exam:
  – Splenomegaly: 90%
  – Hepatomegaly and LAD uncommon
  – Other:
    soft tissue infiltration, vasculitic rash, ascites, effusion
HCL Laboratory Findings

• 60-80% present with pancytopenia
  – Anemia: 85%
  – Thrombocytopenia: 80%
  – Neutropenia: 80%
  – Monocytopenia: 80%
  – Azotemia: 30%
  – Hypergammaglobulinemia: 20%
  – Abn LFTs: 20%
  – Leukocytosis: 10-20%
Establishing the Diagnosis

• Peripheral Smear
  – Hairy cells

• Bone marrow examination
  – Dry tap common
  – Hypercellular
  – HC infiltration diffuse or focal
  – Reticulin stain for fibrosis
  – Flow: pan-B Ags plus CD11c, CD103, CD25
  – TRAP stain
  – Annexin A1
DDx and Other Variants...

- CLL
- B-PLL
- SMZL
- Myelofibrosis
- Other diseases with splenomegaly...

- HCL-Variant
  - Older patients
  - No monocytopenia
  - Less fibrosis
  - Responds poorly to standard therapy
  - Flow
    - Lack of CD25, CD123
    - Expression of CD27
HCL: Who Needs Treatment Anyway?

- Indolent clinical course
- Observation in asymptomatic patients
- Indications for treatment:
  - Significant cytopenias
  - Symptomatic splenomegaly
  - Constitutional symptoms
  - Symptomatic LAD (uncommon)
HCL: History of Treatment Options

• Up until mid-1980s
  Splenectomy: overall survival 4-6 yrs
  IFNα: 80% response, rare CRs *(Quesada et al)*

• Mid 1980s: Purine analogs become standard
  Pentostatin shown to improve CRs *(Spiers et al, Kraut et al)*
  Cladribine high CR rate with a single 7d course *(Piro et al)*
PURINE ANALOGS: Cladribine

• CdA phosphorylated to CdATP
  → DNA strand breaks, inhibition of DNA synthesis, and cell death
• 7-day continuous infusion or 5-day bolus equivalent
• The evidence:
  – Piro et al, 1990: 11/12 pts CR
  – Estey et al, 1992: 36/46 pts CR
  – Others: 76-91% CR rate
  – Largest series: Cheson et al, JCO 1998
    50% CR, 37% PR, 4yr OS 86%
PURINE ANALOGS: Pentostatin

• Irreversible ADA inhibitor
• Variable dose regimens, longer duration
• ECOG study 1992:
  – 50 pts (5mg/m2/d IV x 2d q2wks until max response)
  – ORR 84%, CRR 64%
  – Max response within 6 mo
• Similar results with lower dosing regimens
• Typically effective in IFNα-refractory disease
Choice of Purine Analog: Cladribine vs Pentostatin

- Controversial, institutional decision
- RR, CR rate, 10 yr OS very similar and excellent
- Both prolonged immunosuppression
  - PCP proph, HZV risk
- Second malignancy risk controversial
- Pentostatin
  - Less myelosuppressive if use prolonged dosing?
- Cladribine
  - Ease of administration
  - CD4 recovery time: 40 months (2-CdA) vs 54 months (pentostatin)
Is There Still a Role for Splenectomy or IFNα?

- **Splenectomy**
  - Improves cytopenias; No path. remissions
  - Median response 20 months
  - Role in splenic rupture/infarct or pregnancy

- **IFNα**
  - Improves cytopenias; true CRs uncommon
  - After purine analogs as maintenance
  - To improve counts before purine analog (not routinely used)
Hairy Cell Leukemia: Definition of CR

- Recovery of cytopenias for >1 month
- No evidence of HCL in blood by morphology
- Resolution of organomegaly
- Asymptomatic from their disease
- MRD may still persist...
  - Presence of HCL by flow, IHC, or PCR despite above criteria
What To Do With MRD?

• Dx via immunophenotyping blood or BM
• Molecular studies: clone specific PCR
• May or may not predict future relapse
• MRD eradication:
  – Chemoimmunotherapy 92% success, change in OS unclear (*Ravandi et al Blood 2006*)
  – More clinical trials needed

➔ Unclear what disease characteristics should determine who should be retreated at time of MRD...
Hairy Cell Leukemia Relapse

• Disease control but not cure is common
  – PFS curve for HCL does not plateau
• 30-40% of patients who achieve CR will relapse within 10 years of initial treatment
• Predictors of relapse
  – MRD?
  – Soluble IL-2R
What to do for HCL Disease Relapse?

• Retreat with purine analog
  – Time to CR may dictate whether to switch drugs
• Chemoimmunotherapy: purine analog + rituximab
  – ORR 64-100%, CRR 53-92%, Molecular RR <70%
  – Regimen unclear: concurrent or sequential
  – Trial ongoing: Cladribine plus simultaneous vs delayed rituximab
  – Risks of rituximab: cytokine storm
What to Do for Resistant Disease?

• **Rituximab alone**
  – If contraindication to standard tx
  – 13-55% CR

• **Alemtuzumab**
  – HCs CD52+
  – Concern re: prolonged immunosuppression

• **HSCT in severe cases**

• **Other investigational therapies**
  – Rituximab plus pentostatin or bendamustine
  – Immunotoxin conjugates....
BL22 Immunotoxin

Kreitman et al NEJM 2001
Immunotoxin Conjugates

• LMB-2
  – Immunotoxin against CD25
  – Some PRs in Phase I trial
  – 20% HCL CD25-neg
• BL22
  – Recombinant immunotoxin against CD22
  – Durable remissions in heavily treated pts
  – 41% CR at 50 months
  – Later phase testing underway
• CAT-8015
  – 2nd gen CD22 immunotoxin
  – Phase I trial dose escalation
Figure 1 Recommended treatment schema for HCL

Establish Diagnosis
- Peripheral blood smear/bone marrow
- Immunophenotypic profile by flow cytometry

Follow Clinic Course/Decision to Treat
- Symptoms of bone marrow failure (anemia, infection)
- Splenomegaly with symptoms
- Decline in peripheral blood counts

Initial Treatment with Purine Nucleoside Analog

Confirm Complete Response*

YES
- Follow Patient Until Relapse
- Complete Response > 1 Year
  Consider retreatment with initial therapy or combination purine analog with monoclonal antibody

NO
- Confirm correct diagnosis
- Treat with alternative purine analog with or without monoclonal antibody, or refer for immunotoxin conjugate therapy
- Complete Response < 1 Year
  Same as failure to respond

Now, Back to the Case...

60M from Alaska with LUQ pain, splenomegaly, thrombocytopenia, PB flow with 42% hairy cells

-2005: **INITIAL TREATMENT**: 5-day bolus dose cladribine 0.15 mg/kg/d; also bactrim, levofloxacin proph.

-2006: CBC and spleen size normalized after therapy

-2007: spleen and CBC still normal. PB flow 5% residual HCs (MRD)

-2008: Found to have pancytopenia, sent to SCCA Heme Clinic for further care.

-Seen at SCCA, presenting with fatigue, early satiety, increasing abd girth, night sweats. Spleen 20cm below L costal margin. BM Bx “dry tap.” BM Aspirate: 10% HCs (above phenotype).

→ **RETREATMENT** with chemoimmunotherapy, 7 day CI cladribine 0.1 mg/kg/day CI x 7d plus rituximab, then rituximab maintenance q6mo x 2 years. *First dose rituximab given over 10 hrs in diluted fashion

-2009: Achieved CR. Also repeat bone marrow with no MRD.

-2010: Completed rituximab maintenance.

-Jan 2011: Feels great. Still in CR.
Has Success Spoiled Hairy Cell Leukemia Research? Key Questions Go Unanswered, Despite Big Gains

By David Holzman

Twenty-five years after it was first described, hairy cell leukemia (HCL) was still killing one-third of all its patients within 5 years. But around that time, researchers hit three home runs.

First, an early application of interferon improved survivorship dramatically. Then, in quick succession, two different versions of a class of drugs called nucleoside analogs made further dramatic gains, putting most patients into complete remission. These remissions typically last a decade—and sometimes much longer.

Partly because of that success, HCL is now an orphan in the world of cancer research. Most patients lead fairly normal lives for nearly normal lifespans. Also, HCL is one of the most uncommon cancers, there are just 500–900 new cases in the United States each year, according the Leukemia and Lymphoma Society. That combination removes the urgency that drives young medical researchers to embark on careers in oncology.

In fact, the field is small and actually shrinking, according to Michael R. Grever, M.D., professor of internal medicine at the Ohio State University Medical Center in Columbus.

He and other HCL experts have launched a new consortium, which they hope will spur new interest in HCL, raise awareness of important questions that remain unanswered, and close major gaps in our understanding of the disease.

These questions range from molecular to clinical. Although the prognosis is better than for most other cancers, there is no cure. Some patients eventually relapse, and the drugs lose effectiveness with each successive treatment.

Furthermore, major gaps remain in our understanding of HCL. For example, the normal version of the malignant cell—the hairy cell—is unknown, as are the chemical and biological triggers of HCL. Researchers are ignorant as to why one drug can treat HCL effectively, while most other cancers require multimodality. And when those and other questions might someday lead to actual cures, Grever said.

People with HCL present with the characteristic “hairy” B lymphocytes with their projecting villi, which look like...