Case 1
Eric D. Hsi, MD

Case History
- A 37 year old man presented with 6-8 mm papules on the right shoulder and flank, present for one month.
- Lesions were asymptomatic
- The patient has a past history of seizures and has been on phenytoin for approximately 1 year.

Clinical Appearance

ACCME/Disclosure
Dr. Hsi has no conflict of interest with his USCAP courses, but he does have commercial interest with the following companies: HTG Molecular Diagnostics, Seattle Genetics, Abbvie, Eli Lilly Cellerant Therapeutics.
Other

• PCR studies showed a monoclonal T-cell population
  – Same clonal pattern in both lesions
• Phenytoin was stopped and the lesions regressed.
• Patient is well 5 years later

Drug-induced pseudolymphoma/atypical lymphoid hyperplasia

• Cutaneous drug reactions are among the more common inflammatory reactions in the skin
  – Variety of clinical manifestations: photosensitivity, urticaria, morbilliform rash, erythroderma
  – May mimic of B or T-cell lymphoma
• Can also mimic any inflammatory dermatosis
  – Eczematous, pustular, vesiculobullous, vasculitic, lichenoid, lymphomatous, sclerodermoid patterns
• Lichenoid pattern is common and can be dense
  – Mild spongiosis, exocytosis of lymphocytes
  – Can simulate T-cell lymphomas including MF
  – CD4-rich and loss of pan-T-cell markers have been reported.

Diagnosis

• Drug induced (Dilantin) cutaneous pseudolymphoma

Drug reactions

• Many drugs have been associated with CLH/Pseudolymphoma
  – Antiepileptics: phenytoin, carbamazepine, VPA
  – Antidepressants: fluoxetine, sertraline
  – Others: atenolol, griseofulvin, imatinib, ACE inhibitors, allopurinol, cyclosporine, allopurinol, among others
• Ultimately, high index of suspicion, good clinical history, and willingness to try cessation of a suspected drug is required to demonstrate resolution of lesions (weeks to months)

Sarantopoulous GE et al Am J Clin Pathol 2013
Anticonvulsant Pseudolymphoma Syndrome

- A hypersensitivity reaction to anticonvulsants first recognized in 1950 and described over the years by others.
- Characterized by:
  - Erythematous maculopapular rash or nodules
  - Usually occurs within a few weeks of starting the drug but can occur much later (years)
  - Patients may develop fevers, headache, arthralgia, facial edema, hepatomegaly, eosinophilia, and lymphadenopathy
  - May be fatal if drug is not discontinued

Chaien B et al NEJM 1950

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DDx

- Primary cutaneous CD4+ pleomorphic small medium T-cell lymphoma
  - 2008 WHO provisional entity
  - Presents as an asymptomatic solitary lesion of the head/neck, trunk
  - Usually small plaque/nodule
  - <30% large pleomorphic cells
  - CD4+ lymphoma of Tfh phenotype
    - Expression of PD1, CXCL13, BCL6
    - Often located around B-cells.
    - Monoclonal, EBV negative


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Anticonvulsant Pseudolymphoma Syndrome

- Improvement seen 2-9 weeks after cessation of drug
- Histology may mimic MF
- Features favoring PSL over MF
  - Spongiosis
  - Necrotic keratinocytes
  - Eosinophils in the epidermis
  - Extravasated erythrocytes, papillary dermal edema
  - Mixed inflammatory cells
- TCRG rearrangement positive in 1/8 cases


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DDx

- Tfh markers – are they useful in distinguishing PC CD4+ PSMTCL from other PC TCLs?

- Lymphomatoid drug reaction?
  - No – a case in this series was known to be carbamazepine related and was positive for Tfh markers

DDx

- Studies such as these and known indolent behavior of this provisional entity has caused a rethinking of this entity and the 2016 WHO update will likely change this to:
  - PC CD4+ pleomorphic small medium T-cell lymphoproliferative disorder

Cutaneous “Pseudolymphoma”:
General Patterns and Considerations

- B-cell rich pattern (Cutaneous lymphoid follicular hyperplasia)
  - Reactive B-cell follicles of cutaneous RLH
  - Immune reaction to foreign antigens (bite, stings, tattoo, other trauma, infection such as B. burgdorferi)
  - Variably dense infiltrates that spare epidermis
  - Infiltration of adnexal structures can be seen
  - Bland cells with typical morphology of centrocytes/centroblasts in follicles, features of reactive follicles (tingible body macrophages, polarity, mitoses)
  - Other inflammatory cells (eos suggesting bite or scabies)
  - Intact immune architecture, no phenotypic abnormalities
    - CD20, CD3, CD5, BCL2, CD10, BCL6, CD21, CD43, κ, λ
    - Try and avoid gene rearrangement studies

Gilliam AC. Semin Cutan Med Surg 2000
B-cell pattern

- **DDx of B-cell pattern CLH**
  - **Primary cutaneous MALT-type lymphoma**
    - Dense infiltrate with B-cell of appropriate morphology extending diffusely into interfollicular areas
    - CD43 expression in a minority of cases
    - Plasmacytic differentiation
    - Monoclonal
  - **PC follicle center lymphoma**
    - Usually diffuse infiltrate of centroblasts and large centrocytes
    - Abnormal immune architecture
    - CD10 and/or BCL6 positive B-cells (monoclonal)
    - BCL2 usually negative
    - Some cases with follicular architecture may resemble conventional systemic FL (undetected systemic FL?)

Mirza et al J Clin Oncol 2002
T-cell pattern with questionable relationship to lymphoma

- Pigmented Purpuric Dermatoses
- Pityriasis Lichenoides
  - PLC
  - PLEVA
- Lupus Profundus
- Primary cutaneous acral indolent CD8+ T-cell lymphoid proliferation/lymphoma

T-cell rich pattern

- **Pigmented purpuric dermatosis (PPD)**
  - Petechial bronze discoloration of the skin of lower extremities
  - Known associations with systemic diseases (SLE, RA, liver disease, lymphoid malignancy, hyperlipidemia), drug exposure (NSAIDs, lipid lowering drugs, IFN)
- **Multiple clinicopathologic types**
  - Schamberg disease (cayenne pepper-like lesions on the legs)
  - Majocchi purpura (“Purpura annularis telangiectoides”, erythematous annular patches/plaques on buttocks, trunk, proximal extremities)
  - Gogerot-Blum purpura (lichen planus-like papules with purpura)
  - Lichen aureus (golden indurated plaques over the medial malleolus)
  - Eczematoid purpura of Doucas and Kapetanakis (eczema with a background of purpura)

T-cell pattern - PPD

- Superficial perivascular lymphoid infiltrate with hemorrhage and varying degrees of hemosiderin pigment (free or intracellular in histiocytes/dendritic cells)
  - Lichenoid variants resemble MF
  - Confusion in cases where MF and PPD coexist
  - Cases of PPD reported with epidermotropism, cytologic atypia, & gene rearrangement
    - Some series show up to 50% of cases were monoclonal
- Controversial whether PPD represents a precursor or mimic of MF
- Clinical presentation is important and adherence to criteria for diagnosis of MF
  - Clinical follow-up

Satantouspolous et al Am J Clin Pathol 2012
Sardana et al Int J Dermatol 2004

PPD

Satantouspolous et al Am J Clin Pathol 2012
Sardana et al Int J Dermatol 2004


Pityriasis Lichenoides (PL)

- A papulosquamous dermatitis with spectrum of clinical presentations.
- Unified by general histopathology of a lichenoid infiltrate of varying severity and association with cutaneous lymphoma.
- Occurs in young/adolescent age with male predominance
- 3 variants
  - PLC
  - PLEVA
  - Febrile ulceronecrotic Mucha Habermann Disease

PL

- Pityriasis lichenoides et varioliformis acuta (PLEVA)
  - Acute/subacute presentation of multiple erythematous plaques with ulceration on flexural surfaces, proximal extremities, and trunk
  - Dense interface dermatitis with vacuolar change, exocytosis, epidermal hemorrhage, necrotic keratinocytes and a wedge shaped dermal infiltrate (CD8 predominant cytotoxic T-cells)

PLC

- Pityriasis lichenoides chronica
  - Small erythematous/brown maculopapules with fine scale occurring in crops on the trunk or proximal extremities
  - Band-like dermal lymphoid infiltrate with mild spongiosis, hemorrhage, necrotic keratinocytes, or vesicle formation.
  - Heals over months
    - Hyper/hypopigmentation
    - No scarring

PLEVA

- Heals over weeks to months
- Scarring with hyper/hypopigmentation
- Usually self limited and care is supportive with antimicrobials to avoid secondary infection, topical steroids, phototherapy
- Lymphomas such as MF and LyP have occurred in the setting of PLC/PLEVA
  - Clones can be found in PL suggesting a form of “T-cell dyscrasia”
Febrile ulceronecrotic Mucha Habermann Disease

- Historically a very aggressive variant of PL with generalized purpuric ulcerated and necrotic crusted plaques
  - Approx. 50 cases reported, many as case reports
- Constitutional symptoms, leukocytosis, hyperalbuminemia, elevated LCH and CRP
- Dense ulcerative lymphoid infiltrate with vasculitis, prominent epidermotropic CD8+ T-cell infiltrate and extravasated erythrocytes

Lupus associated panniculitis

- A cutaneous manifestation of LE
- Often occurs with other clinical cutaneous and extracutaneous manifestations of LE
  - May occur in isolation or before overt manifestation of LE
  - Up to 50% of cases occur with no other manifestations of LE
  - 2% of patients with LE will have lupus panniculitis

Lupus panniculitis

- Occurs in females in 3rd to 5th decade
- Presents with tan – violaceous plaques of head/neck, arms, trunk and buttocks
  - Often symmetrical and can ulcerate
- Histopathology
  - Infiltration of subcutaneous fat lobules by lymphocytes, histiocytes and plasma cells with necrosis
    - Fat necrosis
  - Endothelial necrosis, fibrin thrombi may be seen.
  - Lymphoid follicles with reactive germinal centers may be present
  - Histiocytes may contain nuclear debris
  - Interstitial dermal mucin

Lupus panniculitis

-Fatal in 25% of cases
- Treatments include systemic steroids, MTX, biologics (infliximab) with some success.
- Relationship to lymphoma has been the subject of debate
- Resembles primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
  - Fatal adult cases of FUMHC may have been CD8+ AECTCL
  - Pediatric cases more likely to represent PL spectrum?

FUMHD

- Fatal in 25% of cases
- Treatments include systemic steroids, MTX, biologics (infliximab) with some success.
- Relationship to lymphoma has been the subject of debate
- Resembles primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma
  - Fatal adult cases of FUMHC may have been CD8+ AECTCL
  - Pediatric cases more likely to represent PL spectrum?
Lupus panniculitis

- Histopathology
  - Mild atypia
  - Rimming of fat lobules can be seen
  - Immunophenotyping
    - T-cell rich (αβ) CD8 predominance but variable CD4.
    - Loss of pan-T-cell markers such as CD7 can occur and are not helpful
  - Clonality can be seen

Features favoring...

- SCPTCL
  - Moderate to marked cytologic atypia, Ki67 hotspots (foci with Ki67 > 30%), clonality
- Lupus panniculitis
  - Fat necrosis, lymphoid follicles, dermal mucin, moderate/marked PDCs in subcutaneous fat (CD123), serology (ANA or dsDNA+)
- Not discriminatory
  - Karyorrhexis, adipocyte rimming, vasculitis, granulomas, interface dermatitis, plasma cells

Primary cutaneous acral indolent CD8+ T-cell lymphoid proliferation/lymphoma

- First described 2007
  - 4 cases of an indolent dense lymphoid infiltrate of ear in adults (median 58 yrs)
  - Slow growing painless nodule on ear (usually solitary)
  - Undergo spontaneous regression or resolution with excision or RT.
  - Relapse may occur on the opposite ear
- Since then approx. 40 cases reported with realization that they may occur in other acral sites (facial or nonfacial)
Indolent Acral CD8+ LPD

**Histopathology**
- Dense dermal, non-epidermotropic infiltrate
- Small/medium sized cells
- Cytotoxic T-cells
  - CD3, CD8, TIA1, GzB, βF1+
  - May show loss other pan-T cell markers
  - CD30-
  - CD68+ (golgi)*
- Monoclonal

Wobser M et al J Cutan Pathol 2013
Wobser M et al Br J Dermatol 2015*

**Case 2 - History**
- 57 yo woman with inguinal lymphadenopathy present for years

**Indolent Acral CD8+ LPD**
- Excellent outcome with conservative management
  - Surgery alone
  - Radiation therapy

### Table 1: Clinicopathological features of all clinically and histologically classified Indolent CD8+ lymphocytic infiltrates

- Reference
  - Krediet et al 1989
  - Ito et al 1998
  - Fields et al 1998
  - Liu et al 1998
  - Rhee et al 1998
  - Sun et al 2010
  - Landgraf et al 2010
  - Zordi et al 2012
  - Wobser et al 2013
  - Park et al 2015

<table>
<thead>
<tr>
<th>Date</th>
<th>Age</th>
<th>Sex</th>
<th>Duration</th>
<th>Number of lymphocytic infiltrates</th>
<th>Therapy</th>
<th>Outcome</th>
</tr>
</thead>
</table>
**In situ** follicular neoplasia

a.k.a

**in situ** follicular lymphoma

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**“In situ” lymphoma**

- Name derived from the concept of in situ carcinomas
  - *In situ* = in its place
  - Neoplastic cells confined to native microscopic site/compartment
  - Confined to areas limited by basement membranes so that metastasis not yet possible
    - DCIS/LCIS
    - CIS of the uterine cervix
    - CIS of the colon (adenomatous polyps)

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**Tissue Counterpart - FLIS**

- First described 2002
  - 23 patients with focal GCs containing BCL2+ B-cells
  - Monoclonal by LCM
  - BCL2-JH fusion by PCR in 6/14

**Pathology:**
- Undisturbed architecture
- Small centrocyte cytology
- Strong expression of BCL2
- Strong expression of CD10
- Cells limited to GCs
  - Rare cells in IF region or MZ

[Image of pathology images]

Cong et al Blood 2002

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**FLIS**

- 5/23 pts had synchronous FL
- 2 pts had other synchronous CLL or LPL
- 13 remaining patients had f/u:
  - 10 no lymphoma (2-96 mo, median 15.5 mo)
  - 3 developed FL at 3, 13, 72 mo after FLIS

[Image of pathology images]

Cong Blood 2002
FLIS

- In situ localization of FL cells
- A neoplastic condition (monoclonal with BCL2 translocation)
- Can occur with or precede FL
  - May occur as composite process
- Homing and colonization of reactive follicles
  - Rare cells in IF or MZ areas
  - Some follicles with only rare BCL2+ cells.
- Tissue counterpart of circulating FL-like cells?
  - A case has been reported with clonal identity of circulating FL-like cells and FLIS in tissue

Cong Blood 2002
Cheung Leukemia 2006

FLIS vs. partial involvement by FL

- Refinement to distinguish partial involvement by FL vs FLIS.
- FLIS (34 pts)
  - 5 had miscellaneous composite lymphomas
  - 3 cases with prior or coexisting FL
  - 1/21 pts without overt lymphoma developed FL at 29 mo (median f/u 41 mo).
- Partial involvement by FL (23 pts)
  - None with prior dx of lymphoma at time of bx
  - 9/17 who were not treated developed FL
  - 6 pts received rituximab and had not yet developed FL (median f/u 51.5 mo)

Jegalian et al. Blood 2011

How Frequent?

- 1294 reactive lymph nodes from 132 patients
  - Unselected consecutive surgical specimens
- 22 LNs in 3/132 (2.3%) showed FLIS
  - One patient had a LN specimen from 2 years prior that also contained FLIS

Henopp et al Histopathology 2011
Circulating FL cells

- Present in most HI (>50%) at low level (<10^{-5})
- Monoclonal IGH-BCL2 bearing CD27+/IgM+ memory B-cells can be found in healthy individuals.
  - These are cells that demonstrate IGH class switch recombination on the translocated allele
    - CSR is unusual in normal IgM memory B-cells
  - Similar to FL cells that usually show CSR in both alleles but an unusual “downstream class switch” (eg. S\gamma to S\alpha)

Roulland S Leukemia 2006
Roulland S JEM 2006
Vaandrager JW et al Blood 1998

Circulating FL cells in HIs

- These cells slowly increase with age (usually <1 in 10^{-5} cells)
- Dramatically increased in farmers with pesticide exposure
- Cells are clonal or oligoclonal expansions

European Prospective Investigation into Cancer and Nutrition (EPIC) Cohort Study

- Level of t(14;18) in blood predicts overt FL
  - Prediagnostic blood samples from 100 healthy subjects who developed FL and 218 controls tested with sensitive qPCR assay
    - validated in an independent cohort of 65 case participants and 128 controls
    - clonal relationships assessed
  - FL developed from the FLLCs and these cells can be found up to 15 yrs prior to overt FL

Roulland S et al J Clin Oncol 2014

Circulating FL-like cells in HI

- These cells appear to be FL precursor cells
  - Express GC markers such as CD10
  - Overexpress BCL2 transcripts from the translocated allele (rescue from apoptosis)
  - Are frozen at the GC stage
    - Express activation-induced cytidine deaminase (AID)
    - Demonstrate CSR and SHM
      - Source of genomic instability
  - Consistent with a model of a low level naïve B-cell acquiring t(14;18)+
    - Exposed to Ag with germinal center reaction and rescue of low affinity BCRs by BCL2 overexpression
    - Clonal expansion and differentiation to IgM+/CD27+ memory B-cell stage
    - Persistence as circulating FLLC with repeated Ag stimulation, expansion, and genomic instability (AID expression)
    - Progression to symptomatic FL

Agopian JEM 2009
Roulland S et al Adv Immunol 2011
• 23x higher risk of subsequent FL in blood samples for samples with t(14;18) frequency > 10^{-4}, regardless of time to overt FL
  • Not all subjects had detectable fusions (even at diagnosis)

How to manage FLIS?

• FLIS
  – Physical exam
  – Biopsy of suspicious nodal or extranodal site
  – PB flow cytometry
  – CT staging
  – Bone marrow biopsy (in presence of signs/symptoms related to BM involvement and FC positivity)

• FLIS associated with overt lymphoma
  – Stage overt lymphoma type
Management

• If overt lymphoma, treat for that type
• If no overt lymphoma
  – Watchful waiting

Carbone Blood 2011

• WHO 2016 revision
  – In situ follicular neoplasia

History

• 62 year old woman
• Absolute lymphocytosis on routine CBC/Diff
  – WBC 11.5 x 10^9/L, Abs Lymph = 5.2
  – Persistent for 3 months
  – Otherwise asymptomatic
  – Normal Hgb and PLT
• Flow cytometry demonstrated a monoclonal B-cell population
  – CD19+, CD20+ (dim), CD5+, CD23+, FMC7 neg, kappa (dim)
  – Abs count 2.3 x 10^9/L
• FISH trisomy 12

Diagnosis?

• Depends....

Case 3
### Diagnosis?
- Depends...
- No lymphadenopathy
- No history of autoimmune disease
- No associated infection
- No other symptoms

### CLL phenotype MBL
- **Definition**
  - Clonal B-cell population in peripheral blood
    - Kappa or lambda restricted
    - sIg neg on >25% of B-cells
  - CLL phenotype CD5+, CD19+, CD23+, CD20 dim, monotypic Kappa or lambda (dim)
  - ≤ 5 x 10⁹/L monoclonal B-cells
  - No lymphadenopathy or organomegaly, or other feature diagnostic of a B-cell LPD
  - No associated autoimmune/infectious disease

### Dx of CLL: Historical Perspective
- **Better tools = more diagnosis of CLL**
  - 1950s: 10% of CLL cases were identified from routine blood count
  - Definitions of CLL changed, with various groups Rai stage 0, iwCLL, NCI – lowering lymphocyte counts from 15,000 to 5,000 x 10⁹/L
  - Incidence of CLL doubled from 2.6 to 5.4 per 100,000 person years and median survivals increased from 3 to 7 years.
  - Incidence stabilized with widespread use of automated hematology analyzers
  - But along came flow cytometers....
Flow cytometry

- CLL phenotype defined in the 1980s and early 1990s:
  - Ability went from 2-3 color flow in the late 1980s to over 4 in the late 1990s and > 6-10 at present
  - Clinical labs could be expected by the mid-1990s to reproducibly and consistently detect CLL phenotype cells with absolute lymphocyte counts above 5,000/μL (1996 guidelines for CLL per NCI).
  - The ability to detect 1 in 10⁴ to 10⁶ became possible and thus CLL cells were found at extremely low levels
  - A clinical problem because low level CLL phenotype cells were being detected in patients with reactive lymphocytosis and would fit CLL by NCI 1996 criteria
    - Is it appropriate to label these patients with CLL?

MBL

- Numerous groups began population based studies to determine frequency of monoclonal CLL-phenotype cells in various patient populations.

Table 1. Prevalence of CLL-type monoclonal B-cell lymphocytosis (MBL) in population studies. The detected prevalence is highly dependent on the method of detection.

<table>
<thead>
<tr>
<th>Study Group</th>
<th>Median age (y, range)</th>
<th>No. of centers</th>
<th>Flow Cytometry</th>
<th>Exclusions</th>
<th>CLL-type B-cell Lymphocytosis</th>
<th>CLL-type B-cell Lymphocytosis Median %</th>
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<tbody>
<tr>
<td>U.S. Res pop.</td>
<td>70-72</td>
<td>2 0</td>
<td>No</td>
<td>No</td>
<td>N.S.</td>
<td>0.0</td>
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<tr>
<td>U.S. Blood donors</td>
<td>50-56</td>
<td>2 0</td>
<td>No</td>
<td>No</td>
<td>N.S.</td>
<td>0.14</td>
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<tr>
<td>U.K. Hospital</td>
<td>67-90</td>
<td>4 2</td>
<td>Yes</td>
<td>Yes</td>
<td>200</td>
<td>3.0</td>
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<tr>
<td>U.K. Primary care</td>
<td>68-49</td>
<td>4 2</td>
<td>Yes</td>
<td>Yes</td>
<td>200</td>
<td>5.0</td>
</tr>
<tr>
<td>U.K. Hospital</td>
<td>68-49</td>
<td>4 2</td>
<td>Yes</td>
<td>Yes</td>
<td>200</td>
<td>5.1</td>
</tr>
<tr>
<td>U.K. Hospital</td>
<td>68-49</td>
<td>4 2</td>
<td>Yes</td>
<td>Yes</td>
<td>5000</td>
<td>12.0</td>
</tr>
</tbody>
</table>

MBL genetics are that of favorable CLL

Table 1. Chromosomal abnormalities and IGVR Gene Usage and Mutation in Subjects with CLL Phenotype MBL.

<table>
<thead>
<tr>
<th>Chromosomal Abnormalities</th>
<th>CLL Phenotype MBL and Normal Blood Count</th>
<th>CLL Phenotype MBL and Lymphocytosis</th>
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</thead>
<tbody>
<tr>
<td>11q23 Deletion</td>
<td>12/14 (86)</td>
<td>15/18 (94)</td>
</tr>
<tr>
<td>17p Deletion</td>
<td>7/12 (58)</td>
<td>2/3 (67)</td>
</tr>
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<td>7/12 (58)</td>
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</tr>
</tbody>
</table>

MBL population study (4-color, analyzed 5 x 10⁵ cells)
- 1520 outpts. age 62-80 with normal blood counts
  - 5.1% MBL
- 2228 outpt. subjects with ALC >4 x 10⁹/L
  - 13.9% MBL (309)
  - 185 with f/u
    - 28% progressive lymphocytosis
    - 15% with CLL
    - Chemotherapy needed in 7%
    - 4 deaths due to CLL (median f/u 6.8 yrs)

Rawstron AC Hematology 2009

Rawstron NEJM 2008
B-cell ALC predicts development progressive disease (features of CLL or progressive lymphocytosis)

Rawstron *NEJM* 2008

MBL

- These studies have shown there are essentially 2 types of MBL – low vs high (500/μL)

Strati and Shanafelt *Blood* 2015

MBL

- For patients with lymphocytosis and CLL-phenotype MBL, CLL requiring treatment develops at the rate of 1.1%/yr.
- All cases of CLL are preceded by and MBL several years prior to diagnosis
- Risk is low in patients with “low” numbers of MBL cells

Rawstron *NEJM* 2008

Landgren O et al. *NEJM* 2009

Low vs High Count MBL

- Biological differences:
  - *IGHV* rearrangements seen in CLL (4-34, 3-23, 1-69) are underrepresented in low count MBL compared to high count MBL
  - Mutated *IGHV* frequency is higher in low count MBL compared to high count MBL
  - Use of stereotyped CDR3 sequences in low count MBL much less frequent in low count MBL (<5%) compared to high count MBL and CLL (25%)

Strati and Shanafelt *Blood* 2015
Low vs high count MBL

- Clinical differences:
  - Low count rarely progresses
  - Prospective study of 1779 healthy adult from Northern Italy screened with sensitive FC.
  - 138 low count MBL (96 CLL-type, 21 atypical CLL MBL, 20 CD5- MBL)
  - Median f/u 34 mo.
    - Persistent clones in 90% of cases with CLL-type MBL and no progression or other lymphoid malignancy
    - No differences in life expectancy.
  - No specific f/u is required

Differential Diagnosis

- Reactive lymphocytosis
  - Infections (viral) including hepatitis and HIV
  - Autoimmune disease
  - Smoking
  - Hypersensitivity reactions
  - Stress
  - Splenectomy

High Count

- Risk of progression 1-2%/yr
- Annual CBC/Diff and physical exam
- OS does not differ from the age/sex matched general population
- These individuals may be at higher risk of infection requiring hospitalization and malignancy (hematologic and non-hematologic)
  - Biologic risk factors for CLL may help stratify high count MBL but more studies are needed.

MBL Differential Dx

- Persistent polyclonal lymphocytosis
  - Women (40-50), smokers, HLA-DR7
  - Memory B-cells (IgM+, CD27+)
  - Polyclonal B-cells
    - May show isochromosome 3
    - IGH-BCL2 rearrangements (polyclonal) can be detected
    - Usually CD5 negative
      - 21% dim CD5 expression in one series
  - Bilobed lymphocytes

Troussard et al 2008
Semenza and Shanafelt Blood 2015
CD5- MBL

- These exist and may be related to SMZL
- Retrospective study 102 patients from 3 centers
  - Patients with 6 mo persistent lymphocytosis (> 3 x 10⁹/L) or paraprotein
  - No adenopathy/splenomegaly, inflammation, autoimmune disease or cytopenias, no Hep C
  - SMZL phenotype
  - Median f/u 5 years – 85 were stable, 17 progressed (15 developed splenomegaly).
    - Clonal B-cell count, degree of BM infiltration, phenotype or immunogenetic features did not predict progression.
    - Del 7q confined to stable group, complex karyotypes more frequent in progressors.

MBL Differential Diagnosis

- B-cell lymphoma
  - Staging may be required to exclude systemic lymphoma
    - CD5- MBL should be investigated for splenomegaly etc.
  - Non-nodal MCL
    - MBL-like non-nodal MCL
      - Rare cases might be found without any evidence of lymphoma (no lymphadenopathy and splenomegaly)
    - Low level CD5+ monoclonal B-cells, cyclin D1 translocation (FISH, cytogenetics), rare cyclin D1+/SOX11 negative B-cells in BM biopsy

MBL

- WHO 2016 revision
  - Will eliminate option to diagnose CLL with < 5 x 10⁹/L in the absence of extramedullary disease, even if there are cytopenias or disease related symptoms