# Lymphoma and leukemia

## Definition

- Clonal proliferation of hematopoietic progenitor with failed differentiation into mature elements → ↑ blasts in bone marrow and periphery → ↓ RBCs, platelets, and neutrophils

## Epidemiology and risk factors

- Acute myelogenous (AML): ~20k cases/y in U.S.; median age 68 y
- Acute lymphocytic (ALL): ~6k cases/y in U.S.; median age 15 y but 2nd peak in older adults
- Risk factors: radiation, chemo (alkylating agents, topo II inhib), benzene, smoking, ? rising from acquired somatic mutations and clonal hematopoiesis (*NEJM* 2014;371:2477)
- Secondary to acquired hematopoietic dis.: MDS, MPN (esp. CML), aplastic anemia, PNH
- Inherited: Down's, Klinefelter's, Fanconi's anemia, Bloom syndrome, ataxia telangiectasia, Li-Fraumeni, germline mutations in *RUNX1*, *CEBPa*, & *GATA2*

telangiectasia, Li-Fraumeni, germline mutations in RUNX1, CEBPA, & GATA2

## Clinical manifestations

- Cytopenias → fatigue (anemia), infection (neutropenia), bleeding (thrombocytopenia)
- More common in AML
  - Leukostasis (more often when blast count >50,000/μL): dyspnea, hypoxemia, headache, blurred vision, confusion,TIA/CVA, interstitial infiltrates
  - DIC (esp. with APL); leukemic infiltration of skin, gingiva (esp. with monocytic subtypes); chloroma: extramedullary tumor of leukemic cells, virtually any location
- More common in ALL
  - bony/lumbar pain, LAN, hepatosplenomegaly (also in monocytic AML), SVC syndrome
  - CNS involvement (up to 10%): cranial neuropathies, N/V, headache
  - anterior mediastinal mass (esp. in T-cell); tumor lysis syndrome (qv)

## Diagnostic evaluation (*Blood* 2009;114:937)

- Peripheral smear: anemia, thrombocytopenia, variable WBC + circulating blasts (seen in >95%; ⊕ Auer Rods in AML), peripheral flow cytometry for blast origin (ALL vs. AML)
- Bone marrow: >20% blasts; mostly hypercellular; test for cytogenetics and flow cytometry
- Presence of certain cytogenetic anomalies, eg, t(15;17), t(8;21), inv(16) or t(16;16), are sufficient for dx of AML *regardless of the blast count*
- ✔ for tumor lysis syndrome (rapid cell turnover): ↑ UA, ↑ LDH, ↑ K, ↑ $PO_4$, ↓ Ca
- Coagulation studies to r/o DIC: PT, PTT, fibrinogen, D-dimer, haptoglobin, bilirubin

- LP (w/ co-admin of intrathecal chemotherapy to avoid seeding CSF w/ circulating blasts) for Pts w/ ALL (CNS is sanctuary site) and for Pts w/ AML w/ CNS sx
- TTE if prior cardiac history or before use of anthracyclines
- HLA typing of Pt, siblings > parents/children for potential allogeneic HSCT candidates

# ACUTE MYELOGENOUS LEUKEMIA (AML; *LANCET* 2018;392:593)

## Classification (WHO; *Blood* 20[1]6;[1]27:2391)

- Features used to confirm myeloid lineage and subclassify AML to guide treatment: morphology: blasts, ⊕ granules, ± Auer rods (eosinophilic needle-like inclusions)
- Immunophenotype: precursor: CD34, CD45, HLA-DR; myeloid: CD13, CD33, CD117; monocyte: CD11b, CD64, CD14, CD15
- Prognosis: *age*, prior *antecedent MPN/MDS* and *genetics* (cytogenetics + molecular mutation status) are key independent risk factors

## Prognosis

- CR achieved in 70–80% of Pts <60 y and in 40–50% for Pts >60 y
- Overall survival variable, depends on prognostic factors: ranges from <10% of older Pts w/ poor-risk tumor genetics to >65% for younger Pts w/ favorable prognostic factors

## Acute promyelocytic leukemia (APL) (*Blood* 2009;113:1875)

- Rare, ~8% of AML in U.S.; >90% cure rates
- Atypical promyelocytes (large, granular cells; bilobed nuclei) in blood and bone marrow
- Defined by translocation of retinoic acid receptor: t(15;17); *PML-RARA* (>95% of cases)
- Medical emergency with DIC and bleeding common
- Remarkable responses to all-*trans*-retinoic acid (ATRA) & arsenic trioxide (ATO), which induce differentiation of leukemic blasts. ∴ early initiation as soon as APL *suspected*
- Non-high-risk APL: ATRA + ATO (induction + 4 cycles consolidation) → CR ~100%; event-free survival 97% and overall survival 99% at 2 y (*NEJM* 2013;362:111)
- High-risk APL: WBC >10k at diagnosis. No clear consensus. In general, chemo (anthracycline or gemtuzumab ozogamicin) added to ATRA + ATO induction and consolidation.
- Differentiation (ATRA) syndrome: ~25% of Pts; fever, pulm infiltrates, SOB, edema, HoTN, AKI; tx w/ dexamethasone 10 mg bid, supportive care (eg, diuresis) (*Blood* 2008;113:775)

# ACUTE LYMPHOBLASTIC LEUKEMIA (ALL)

## Classification

- Lymphoblastic neoplasms may present as acute leukemia (ALL) with >20% BM blasts or as lymphoblastic lymphoma (LBL) w/ mass lesion w/ <20% BM blast
- Morphology: no granules (granules seen in myeloid lineage)
- Cytochemistry: ⊕ terminal deoxynucleotidyl transferase (TdT) in 95% of ALL
- Immunophenotype

  Precursor: CD34, TdT

  B: CD19; variable CD10, CD22, CD79a

  T: CD1a, CD2, cytoplasmic CD3, CD5, CD7

# LYMPHOMA

## Definition

- Malignant disorder of lymphoid cells that reside predominantly in lymphoid tissues
- Generally characterized as Hodgkin lymphoma (HL) or non-Hodgkin lymphoma (NHL)

## Clinical manifestations

- Lymphadenopathy (nontender)
  - HL: Reed-Sternberg (RS) cells; superficial (usually cervical/supraclavicular) ± mediastinal LAN; nodal disease with orderly, anatomic spread to adjacent nodes
  - NHL: diffuse; nodal and/or extranodal disease with noncontiguous spread; symptoms reflect involved sites (abdominal fullness, bone pain)
- Constitutional ("B") symptoms: fever (>38°), drenching sweats, ↓ weight (>10% in 6 mo)
  - HL: periodic, recurrent "Pel-Ebstein" fever; 10–15% have pruritus; ~35% "B" symptoms
  - NHL: "B" symptoms vary between subtypes, ~15–50%

## Diagnostic and staging evaluation

- Physical exam: lymph nodes, liver/spleen size, Waldeyer's ring, testes (~1% of NHL), skin
- Pathology: excisional lymph node bx (not FNA b/c need surrounding architecture) with immunophenotyping and cytogenetics; BM bx or PET (except in HL clinical stage IA/IIA w/ favorable features or CLL by flow); LP if CNS involvement clinically suspected
- Lab tests: CBC, BUN/Cr, LFTs, ESR, LDH, UA, Ca, alb; ✔ HBV & HCV (and must ✔ HBsAg & anti-HBc if planning rituximab Rx, b/c can lead to HBV reactivation); consider HIV, HTLV, & EBV serologies and connective tissue diseases autoAbs
- Imaging: PET-CT scans b/c CT alone does not reliably detect spleen/liver involvement (espec. in HL, DLBCL). PET response to Rx can be prognostic & possibly guide Rx (*NEJM* 2015;372:1598 & 2016;374:2419). Head CT/MRI *only* if neurologic symptoms.

| Ann Arbor Staging System with Cotswolds Modifications | |
|---|---|
| Stage | Features |
| I | Single lymph node (LN) region |
| II | ≥2 LN regions on the same side of the diaphragm |
| III | LN regions on both sides of the diaphragm |
| IV | Disseminated involvement of one or more extralymphatic organs |
| Modifiers: A = no symptoms; B = fever, night sweats or weight loss; X = bulky disease = greatest transverse diam. of mediastinal mass/max diam. of chest wall >1/3 on CXR or >10 cm if in abd; E = involves single contiguous extranodal site; H = hepatic; S = splenic | |

# HODGKIN LYMPHOMA (HL) (*Am J Hematol* 2018;93:704)

## Epidemiology and risk factors

- ~9,000 cases/y; bimodal distribution (15–35 & >50 y); ↑ ♂; role of EBV in subsets of HL, esp. immunocompromised patients (eg, HIV)

## Pathology

- Affected nodes show RS cells (<1%) in background of non-neoplastic inflammatory cells
- Classic RS cells: bilobed nucleus & prominent nucleoli with surrounding clear space ("owl's eyes"). RS cells are clonal B-cells: CD15+, CD30+, CD20– (rarely +).

| WHO Histologic Classification of Classical HL | | |
|---|---|---|
| Nodular sclerosis | 60–80% | Collagen bands; frequent mediastinal LAN; young adults; female predominance; usually stage I or II at dx |
| Mixed cellularity | 15–30% | Pleomorphic; older age; male predominance; ≥50% stage III or IV at presentation; intermediate prognosis |
| Lymphocyte rich | 5% | Abundant normal-appearing lymphocytes; mediastinal LAN uncommon; male predominance; good prognosis |
| Lymphocyte depleted | <1% | Diffuse fibrosis and large numbers of RS cells; older, male patients; disseminated at dx; seen in HIV; worst prognosis |

# NON-HODGKIN LYMPHOMA (NHL)

## Epidemiology and risk factors

- ~70,000 new cases/y; median age at dx ~65 y; ♂ predominance; 85% B-cell origin
- Associated conditions: immunodeficiency (eg, HIV, posttransplant); autoimmune disorders (eg, Sjögren's, RA, SLE); infection (eg, EBV, HTLV-I, *H. pylori*)
- Burkitt lymphoma: (1) endemic or African (jaw mass, 80–90% EBV-related); (2) sporadic or American (20% EBV-related); (3) HIV-related

**WHO Classification of Lymphoid Malignancies** (*Blood* 2016;127:2375)

| Type | Examples | Associated Abnormalities |
|---|---|---|
| Mature B cell ↑ increasing aggressiveness | Burkitt's lymphoma | *8q24, c-MYC* |
| | Diffuse large B-cell lymphoma (DLBCL) | *BCL2, MYC, MLL2, CREBBP, etc.* |
| | Mantle cell | *t(11; 14) BCL1-IgH* → cyclin D1 |
| | Marginal zone lymphoma (nodal, extranodal [MALT ✓ *H. pylori*], splenic) | *AP12-MALT1 & BCL-10-Ig enh* |
| | Hairy cell leukemia (⊕ TRAP) | *BRAF V600E* |
| | Follicular lymphoma | *IGH-BCL2, MLL2* |
| | CLL/small lymphocytic lymphoma | *IGVH, ZAP70, TP53, SF3B1, etc.* |
| Mature T cell & NK cell | Peripheral T-cell lymphoma | *TET2 and DNMT3A* |
| | Mycosis fungoides (cutaneous lymphoma)/ Sézary syndrome (+ LAN) | |
| | Anaplastic large-cell lymphoma | Some *ALK1* ⊕ |
| | Angioimmunoblastic T-cell lymphoma | |

# SMALL LYMPHOCYTIC LYMPHOMA (SLL) OR CHRONIC LYMPHOCYTIC LEUKEMIA (CLL)

## Definition (*NEJM* 2005;352:804; *Blood* 2008;111:5446)

- Monoclonal accumulation of functionally incompetent mature B lymphocytes
- CLL (>5000/μL malignant cells) & small lymphocytic lymphoma (SLL; <5000/μL malignant cells, with + LAN ± splenomegaly) classified as same disease
- Monoclonal B lymphocytosis: resembles but does not meet CLL criteria, observe

## Epidemiology and risk factors

- ~15,000 new cases/y; median age at dx is 71 y; most common adult leukemia
- ↑ incidence in 1st-degree relatives; no known association with radiation, chemicals, drugs

## Clinical manifestations

- Symptoms: often asx & identified when CBC reveals lymphocytosis; 10–20% p/w fatigue, malaise, night sweats, weight loss (ie, lymphoma "B" sx)
- Signs: lymphadenopathy (80%) and hepatosplenomegaly (50%)
- Autoimmune hemolytic anemia (AIHA) (~10%) or thrombocytopenia (ITP) (~1–2%)
- Hypogammaglobulinemia ± neutropenia → ↑ susceptibility to infections
- Bone marrow failure in ~13%; monoclonal gammopathy in ~5%
- Aggressive transformation: ~5% develop Richter's syndrome = transformation into high-grade lymphoma (usually DLBCL) and sudden clinical deterioration

## Diagnostic evaluation (see "Lymphoma" for general approach)

- Peripheral smear: lymphocytosis (>5000/μL, mature-appearing small cells) "smudge" cells from damage to abnl lymphs from shear stress of making blood smear

- Flow cytometry: clonality with dim surface Ig (sIg); CD5+, CD19+, CD20(dim), CD23+. CD38+ or ZAP70+ a/w unmutated Ig variable heavy chain region & worse prognosis.
- Bone marrow: normo- or hypercellular; infiltrated w/ small B-cell lymphocytes (≥30%)
- Lymph nodes: infiltrated w/ small lymphocytic or diffuse small cleaved cells = SLL
- Genetics: del 11q22-23 & 17p13 unfavorable; trisomy 12 neutral; del 13q14 and mut *IgVH* favorable. Nine significantly mutated genes, including *TP53*, *NOTCH1*, *MYD88*, and *SF3B1*. Key role for spliceosome mutations (*NEJM* 2011;365:2497; *JCI* 2012;122:3432).

| CLL Staging | | | | |
|---|---|---|---|---|
| **Rai System** | | **Median Survival** | **Binet System** | |
| **Stage** | **Description** | | **Description** | **Stage** |
| 0 | Lymphocytosis *only* | >10 y | <3 node areas | A |
| I | ⊕ lymphadenopathy | 7–10 y | >3 node areas | B |
| II | ⊕ hepatosplenomegaly | | | |
| III | ⊕ anemia (not AIHA) | 1–2 y | Anemia or thrombocytopenia | C |
| IV | ⊕ thrombocytopenia (not ITP) | | | |

## Treatment (*Lancet* 2018;391:1524)

- No treatment unless: Rai stage III/IV, Binet stage C, disease-related sx, progressive disease, AIHA or ITP refractory to steroids, recurrent infections