PATHOLOGY OF BLOOD AND LYMPHATIC SYSTEM-8

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BURKITT LYMPHOMA

- Most common NHL in children
- Three types:

1) Endemic in parts of Africa (100% EBV +)
2) Sporadic in the rest of the world (20% EBV +), latent infection
3) Immunodeficiency associated BL

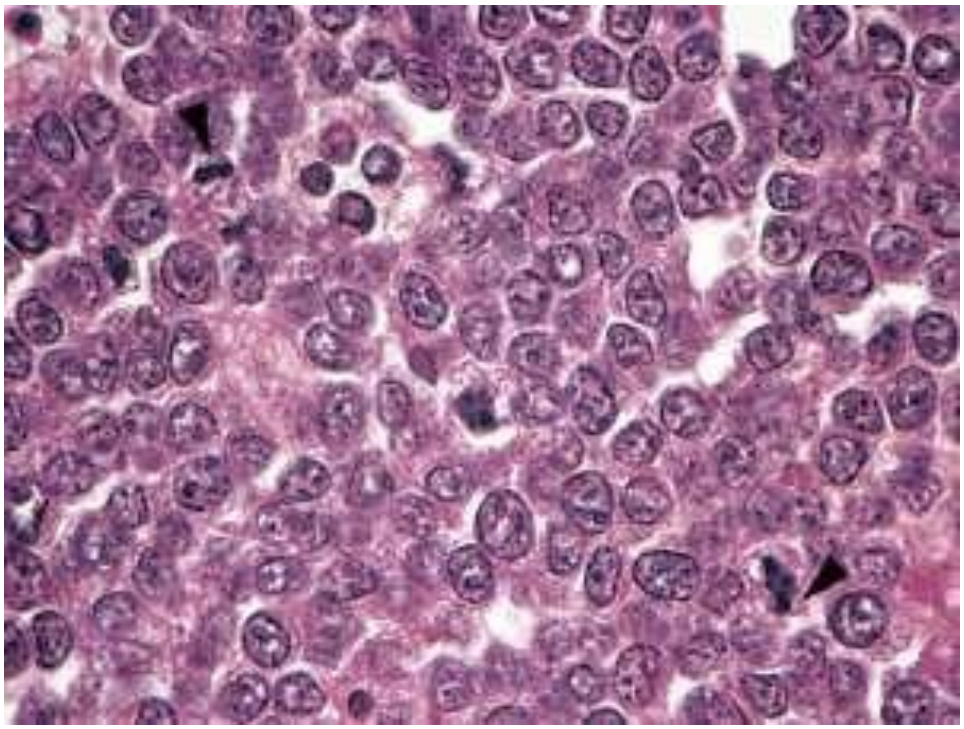
- Extranodal disease: jaw (endemic), terminal ileum, retroperitoneum, ovary, CNS (sporadic), sometimes leukemic

PATHOGENESIS

- t(8;14) MYC→IgH
- Overexpression of MYC transcription factor, potent regulator of Warburg metabolism (aerobic glycolysis)
- Neoplastic lymphocytes are B-cells of germinal center origin (CD20, Bcl6)
- Aggressive, but responsive to chemotherapy

MORPHOLOGY

- Intermediate size cells
- Monomorphic
- Round or oval, multiple small nucleoli
- Lipid vacuoles in cytoplasm
- Very high mitosis, tangible body macrophages engulfing nuclear debris



- Neoplastic lymphocytes are monotonous and uniform, multiple small nucleoli, brisk mitosis

EXRANODAL MARGINAL ZONE LYMPHOMA

- Indolent B-cell lymphoma
- Second most common lymphoma in extranodal sites in adults
- Arises in the setting of chronic inflammation
- Can complicate autoimmune disease in localized areas (Hashimoto thyroiditis, Sjogren syndrome)
- Can complicate Helicobacter pylori-chronic gastritis
- Infiltrate the epithelium and causes destruction

MANTLE CELL LYMPHOMA

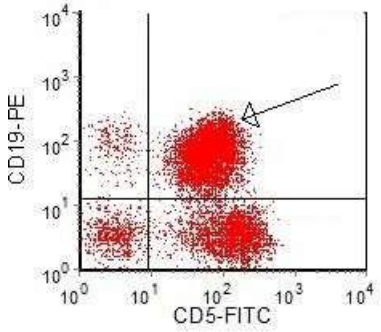
- Arises from naïve B-cells in mantle zone
- Most commonly in older men
- t(11;14) that fuses cyclin D1 gene to IgH locus
- Overexpression of cyclinD1, promote progression of cell cycle
- Affects LNs, Waldeyer ring
- Commonly involve BM, blood in 20%, sometimes in GIT, appears as submucosal nodules (lymphomatoid polyposis)
- Morphology: small centrocytes, but in diffuse pattern

SMALL LYMPHOCYTIC LYMPHOMA/ CHRONIC LYMPHOCYTIC LEUKEMIA

- Low-grade B-cell neoplasm
- Affects elderly
- Can arise in LNs and solid tissue (SLL), or in BM and peripheral blood (CLL)
- Most common leukemia in adults, while SLL represents only 4% of NHL
- Not common in Asia

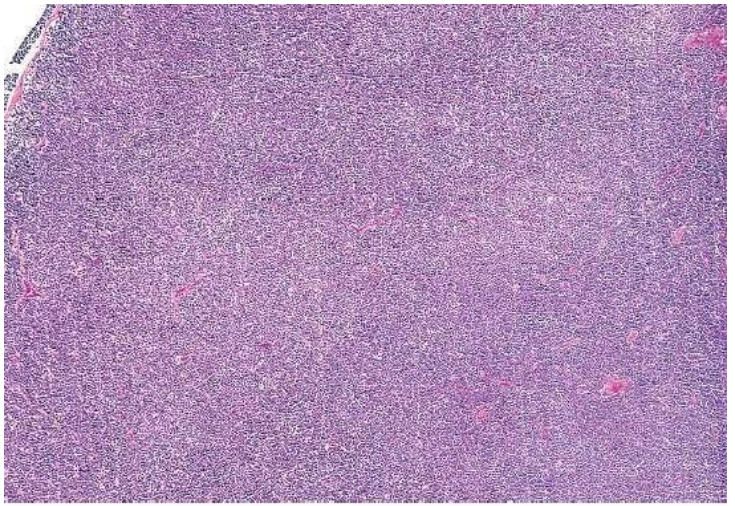
PATHOGENESIS

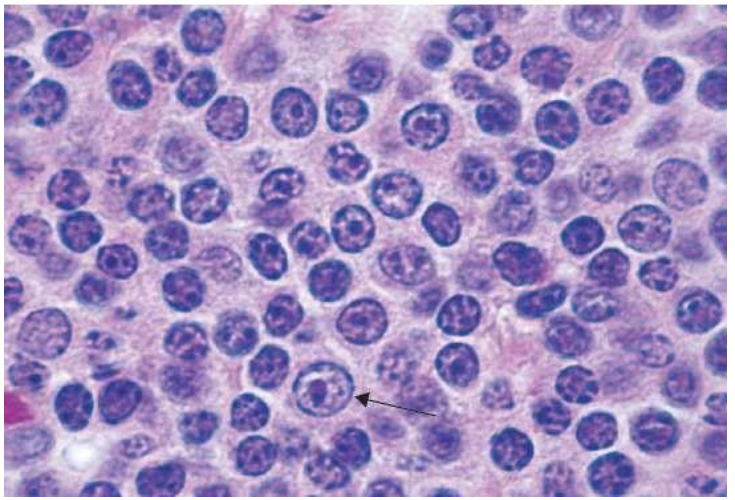
- Increased Bcl2 protein, secondary to deletion mutation in genes encoding micro-RNAs that are negative regulators of Bcl2
- A surface immunoglobulin called B-cell receptor (BCR), is autonomously active, activating a intermediary called Bruton tyrosine kinase (BTK) that activates genes promoting cell survival
- Chromosomal translocation is rare
- Lymphoma cells express CD20, Bcl2 and CD5



MORPHOLOGY OF SLL

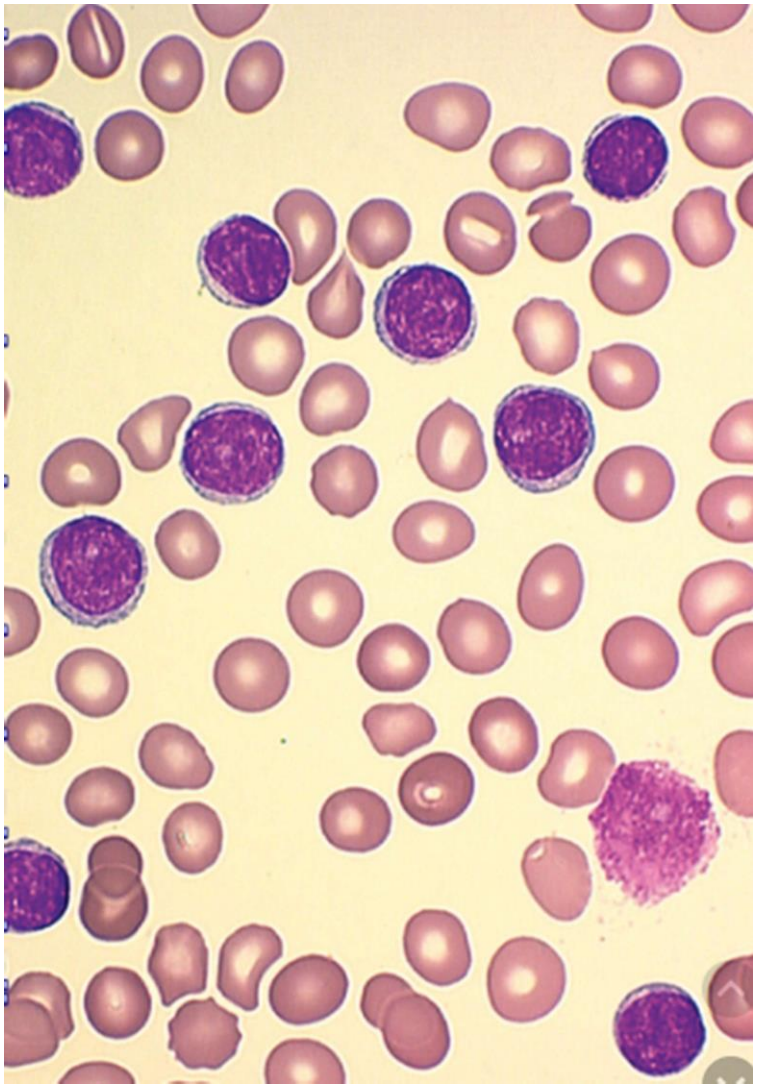
- LN shows effacement of architecture
- Most of neoplastic cells are small in size, round, dark chromatin, along with few large cells with central prominent nucleolus (prolymphocyte)
- Proliferation centers: focal areas containing large number of prolymphocytes and increased mitosis





MORPHOLOGY OF CLL

- Leukemic cells appear similar to lymphocytes
- Occasional prolymphocytes
- Smudge cells



CLINICAL FEATURES

- Many patients are asymptomatic
- Leukocytosis can reach very high levels (>200,000)
- 50% have generalized lymphadenopathy and hepatosplenomegaly
- Immune dysfunction is common, by suppressing normal B-cells, resulting in hypogammaglobulinemia (50% of patients)
- Anemia: 15% of patients develop auto antibodies against RBCs and platelets (cold type), secreted by normal B-cells
- Thrombocytopenia: similar to ITP
- Variable outcome: many patients have similar survival to general population. In contrast, P53 mutation makes prognosis worse
- Richter transformation: predominance of large cells, patients survive <1 year

PRECURSOR B AND T CELL NEOPLASMS

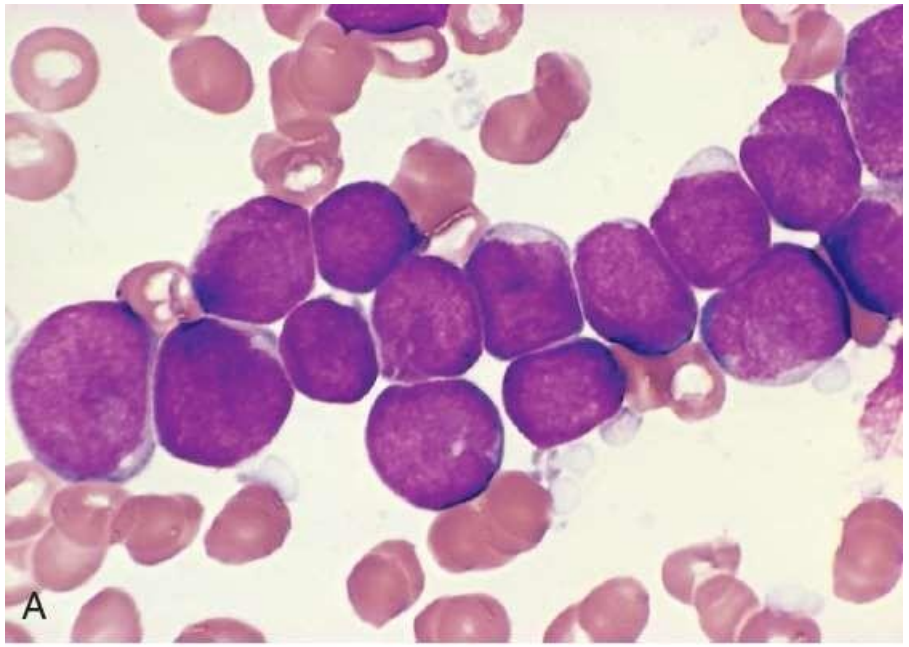
- Lymphoblastic lymphoma when occurs in solid tissue (T>B)
- Acute lymphoblastic leukemia when circulates peripheral blood and involve bone marrow (B>T)
- B-ALL is the most common childhood malignancy
- Neoplastic cells are lymphoblasts, the most immature lymphoid cell. Aggressive neoplasms, express CD34 and TDT
- T-ALL is less common, presents in adolescents, involving thymus, more common in boys
- B-ALL tends to disseminate to solid organs (brain, testis, spleen)

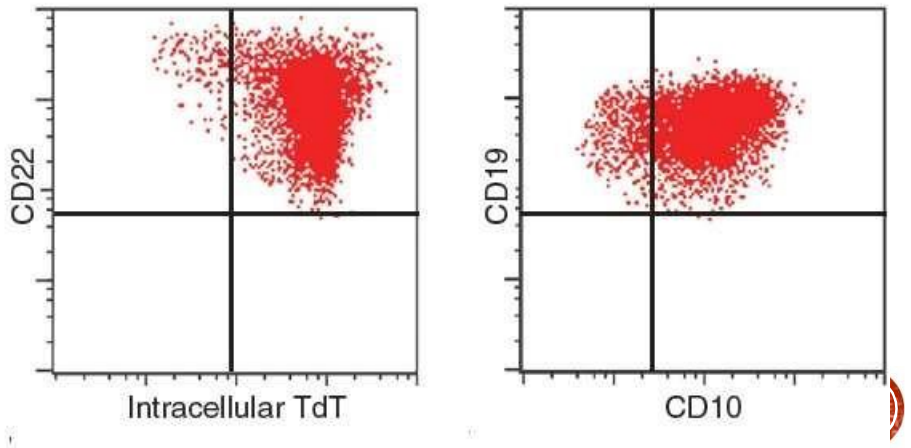
PATHOGENESIS

- Mutations in transcription factors for genes responsible for maturation of blasts
- In T-LL: 70% have mutations in NOTCH1 gene
- In B-LL, mutation in PAX5 gene
- Mutations in RAS signaling and tyrosine kinase proteins promoting cell survival
- Most childhood B-ALL have hyperdiploidy (>50 chromosomes) and t(12;21), involving ETV6 and TUNX1 genes, creating new transcription factor
- Adult B-ALL exhibits t(9;22) between ABL and BCR genes, similar to chronic myeloid leukemia, creating a new tyrosine kinase protein (imatinib)
- T-ALL shows mutation in PTEN gene (tumor suppressor) and CDKN2A (promotes cell cycle)

MORPHOLOGY OF ALL

- Blasts are large, high N/C ration
- Chromatin is open (pale)
- Nucleolus sometimes present
- Cytoplasm is not granular





CLINICAL FEATURES

- Anemia, thrombocytopenia
- Damage to solid organs secondary to leukemic infiltration
- Favorable prognostic factors in B-ALL: hyperdiploidy, low WBC count, age between 2-10 years
- Poor prognostic factors in B-ALL: age < 2 years, age in adolescents or adults, WBC count >100k

PLASMA CELL MYELOMA

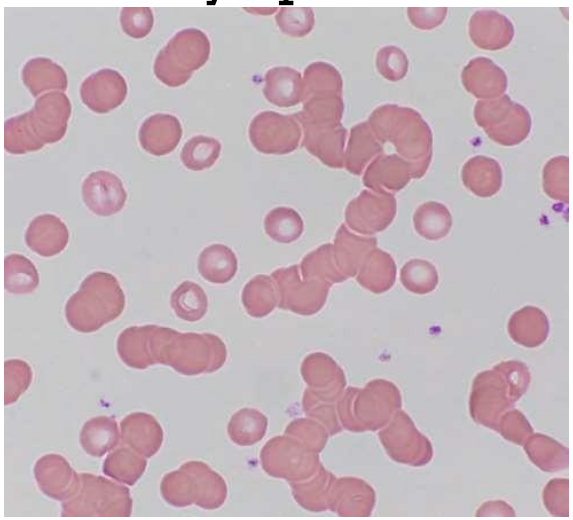
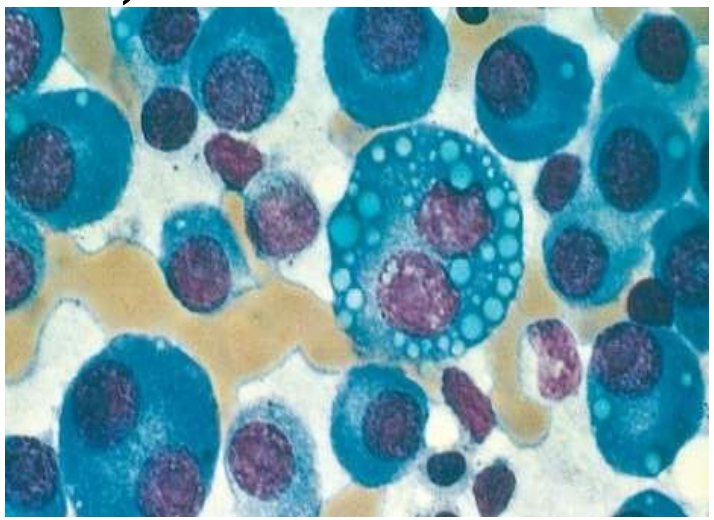
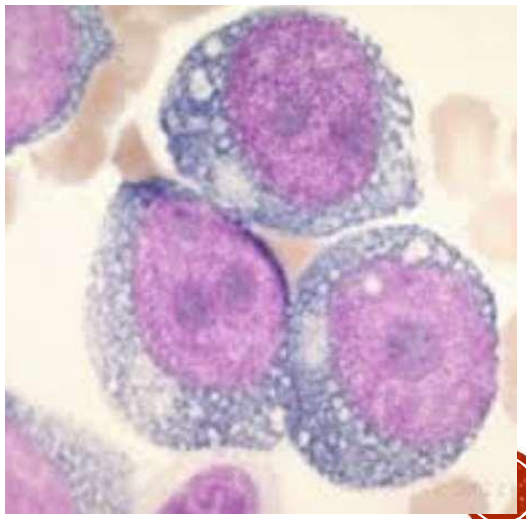
- AKA multiple myeloma
- Common neoplasm
- Commonly in elderly, more common in men, African origin
- Malignant plasma cells secrete monoclonal protein (M protein), most commonly IgG (60%), then IgA (20-25%), followed by other types.
- Sometimes only light chain (kappa or lambda), can be detected in urine (Bence Jones proteins)

PATHOGENESIS

- t(11;14) IgH-cyclinD1 and cyclinD3
- MYC gene mutation occurs late in disease
- IL-6 is important is plasma cell survival, secreted from BM macrophages and fibroblasts
- Malignant plasma cells activate expression of receptor activator of NF-kB ligand (RANKL), that activates osteoclasts, causing bone resorption. Other products inhibit osteoblast function (hypercalcemia and pathologic fracture)
- Suppression of normal B-cell function
- Directly inhibits erythropoiesis (early onset anemia)
- Renal failure: obstruction to distal collecting tubules by proteinaceous cast (Bence Jones protein, immunoglobulin, albumin). Hypercalcemia produces kidney stones, causing further obstruction and renal infection

MORPHOLOGY

- Peripheral blood: RBCs show rouleaux formation
- BM: increased number of plasma cells (>10% of bone marrow cells)
- Morphologically might resemble normal plasma cells, or become abnormal (prominent nucleoli, multinucleation, cytoplasmic vacuoles)

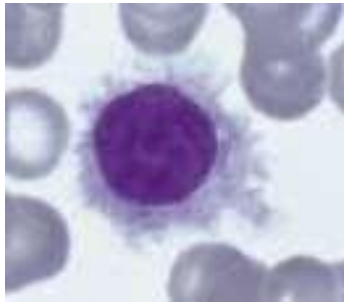




CLINICAL AND LABORATORY FINDINGS

- Very high ESR
- CRAB (hypercalcemia, renal failure, anemia, bone fracture)
- Amyloidosis: occurs in few patients, secondary to deposition of light chain (AL-amyloid)
- In advanced disease: pancytopenia, plasma cell leukemia, visceral damage
- Slowly growing, not curable with conventional chemotherapy
- Lenalidomide: inhibits oncogenic proteins
- Proteasome inhibitors: inhibit degradation of misfolded proteins. When accumulate, cause apoptosis in plasma cells

HAIRY CELL LEUKEMIA

- Uncommon low-grade B-cell leukemia
- Affects older patients, more common in men, smokers
- Leukemic cells are few in number, have prominent cytoplasmic projections
- Splenomegaly, pancytopenia (Leukemic cells heavily infiltrate BM and spleen)
- Leukemic cells are biologically active, inhibit hematopoiesis and cause bone marrow fibrosis
- LN involvement is very rare
- Mutation in serine/threonine kinase BRAF gene
- Very sensitive to chemotherapy

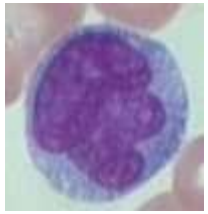


PERIPHERAL T-CELL LYMPHOMA

- Most common mature T-cell lymphoma
- Aggressive, poor prognosis
- Neoplastic cells secrete inflammatory cytokines, causing severe inflammation
- Positive for CD2, CD3, CD5, CD7

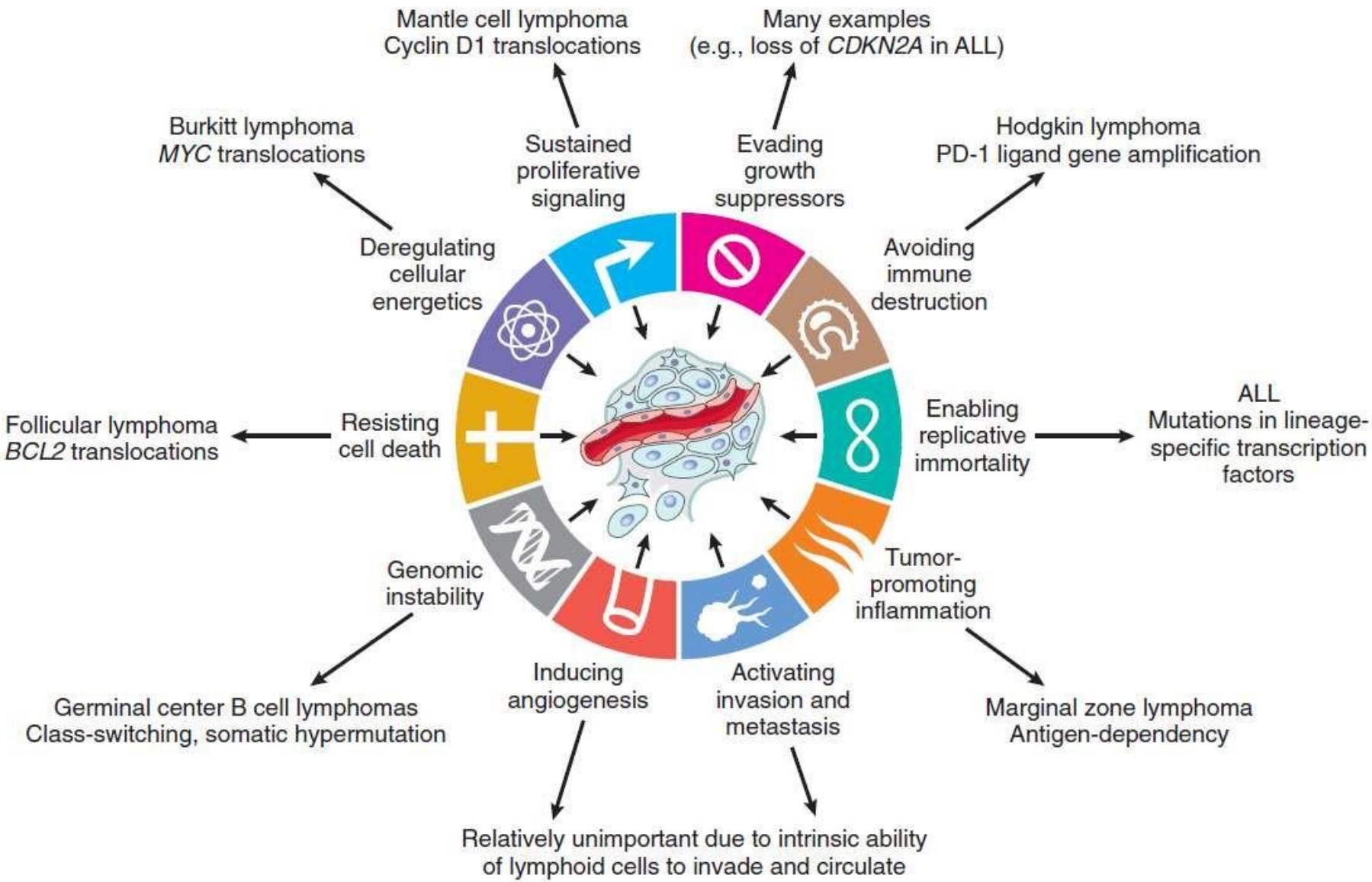
MYCOSIS FUNGOIDES AND SEZARY SYNDROME

- Neoplastic CD4+ T-cells, that home to skin
- Patients present with erythema, progressive to plaque then tumor
- Neoplastic lymphocytes have irregular nuclear membrane (cerebriform), affecting epidermis and dermis.
- With disease progression, lymphoma disseminates to LNs and viscera
- Sezary syndrome: a variant of MF, patients present initially with widespread erythema and blood leukemia of neoplastic cells (Sezary cells)



ADULT T-CELL LEUKEMIA/LYMPHOMA

- Neoplastic CD4+ T-lymphocyte
- Caused by a retrovirus; human T-cell leukemia virus 1 (HTLV-1)
- Endemic in Japan, Caribbean basin, West Africa and some parts of South America
- Sporadic everywhere
- Virus is transmitted through body fluids (blood, breastfeeding, sexual intercourse)
- 5% of carrier develop neoplasm, after a latent period of 40-60 years
- Tax protein is essential for viral mRNA transcription, also interacts with PI3 kinase and cyclin D, represses expression of CDK inhibitors, and activates NF-kB, all promote cell survival. Tax also causes genomic instability, inhibiting DNA-repair
- Patients present with skin lesions, lymphadenopathy, lymphocytosis, hepatosplenomegaly and hypercalcemia
- Neoplastic cells express CD25 (IL-2 receptor)
- Poor prognosis


Mantle cell lymphoma
Cyclin D1 translocations
Many examples
(e.g., loss of *CDKN2A* in ALL)
Burkitt lymphoma
MYC translocations
Sustained proliferative signaling
Evading growth suppressors
Hodgkin lymphoma
PD-1 ligand gene amplification
Deregulating cellular energetics
Avoiding immune destruction
Follicular lymphoma
BCL2 translocations
Resisting cell death
Enabling replicative immortality
ALL
Mutations in lineage-specific transcription factors
Genomic instability
Tumor-promoting inflammation
Germinal center B cell lymphomas
Class-switching, somatic hypermutation
Inducing angiogenesis
Activating invasion and metastasis
Marginal zone lymphoma
Antigen-dependency
Relatively unimportant due to intrinsic ability of lymphoid cells to invade and circulate