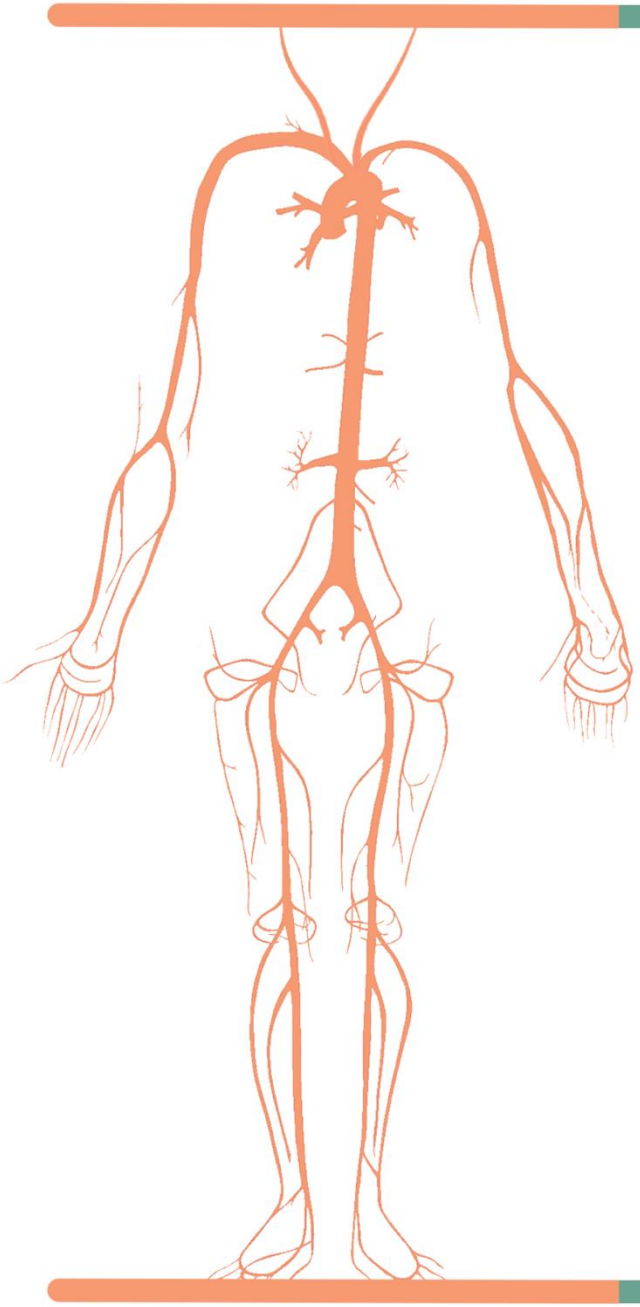
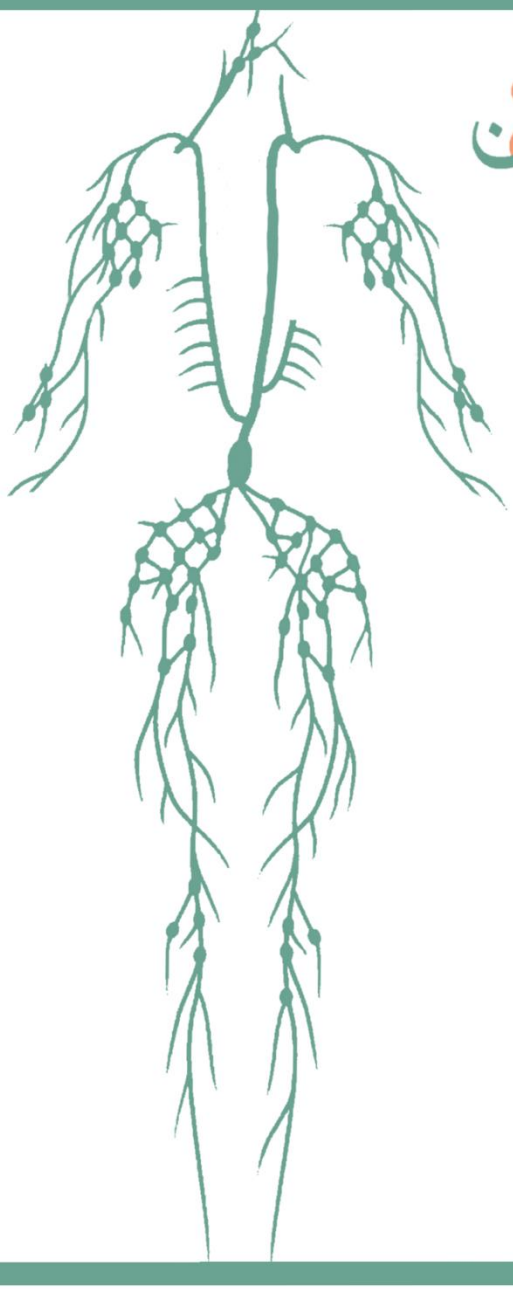
Pathology

HematoLymphatic





Title: Sheet 8 – NHL contd, & PB&T neoplasms

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Burkitt Lymphoma

THE most common NHL in children

- Three types:
  i. Endemic in parts of **Africa**
  100% of cases are associated with EBV
  ii. Sporadic in the **rest of the world** (20% EBV +),
  results from a latent infection
  iii. Immunodeficiency (+ HIV) associated BL

> *Remember:*
>
> HODGKIN LYMPHOMA is THE MOST common lymphoma in children

- Burkitt lymphoma is an **Extranodal lymphoma** [primarily arises outside lymph nodes]: jaw [most common in endemic] → it causes jaw enlargement and disfigurement of the face.
  Terminal ileum, retroperitoneum, ovary, CNS → [sporadic or immunodeficiency].
  - Sometimes manifests as a leukemic disease (in the blood and BM)

❖ Pathogenesis:

- t(8;14) MYC→ IgH
  - MYC gene is translocated to chromosome 14 next to IgH gene, which as we took in the previous lecture is very active

This causes Overexpression of MYC transcription factor, a potent regulator of Warburg metabolism [which is an alternative to normal aerobic glycolysis. Instead, cancerous cells depend on other pathways that result in more **anabolic activity** (building/ energy consuming)]

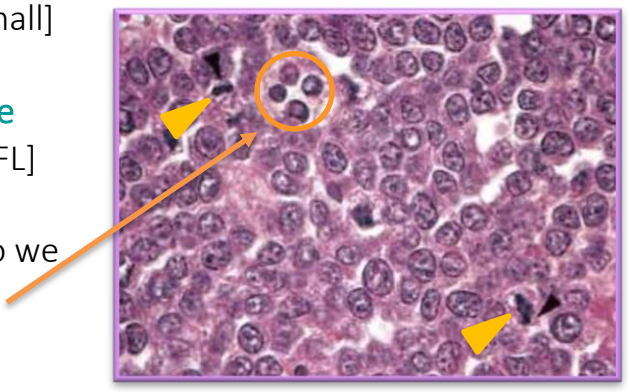
[Remember: in cancer, cells want to mainly grow and divide, not do normal functions, and that is why they need this form of modified cellular metabolism]

- Neoplastic lymphocytes originate from **B-cells of germinal center**,so they express their markers → CD20 [B-cell marker], Bcl6 and CD10 [germinal center markers]
- Aggressive, but responsive to chemotherapy [high proliferative activity]

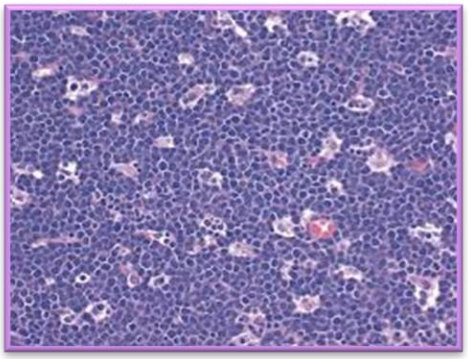
❖ Morphology:

- Intermediate size cells [not Giant nor small]
- Monomorphic [all have the same appearance] ***look at the picture to the side**
- Round or oval nuclei [unlike DLBCL and FL] with Multiple small nucleoli
- Very high mitosis, and a lot of apoptosis; so we see tangible body macrophages engulfing nuclear debris

The yellow arrow heads are pointing at mitotic bodies



- In the leukemic phase, we can find Lipid vacuoles in the cytoplasm



↳ In low power: this cancer has a characteristic look called the starry sky → the macrophages look white surrounded by the dark color of other cells.

This is **THE FASTEST** growing human cancer, its duplication time of tumor volume is only 8 Hrs!!

Extra-nodal marginal zone lymphoma

- Name breakdown:
  Extra nodal: Predominantly arises **outside the lymph nodes**
  Marginal zone: comes after the germinal center, cells in it are **more mature** and they precede the plasma cell formation [The tumour has a B-cell origin]
  - ↳ **Second most common lymphoma in extranodal sites in adults after DLBCL**

- Indolent
- Arises in the setting of chronic inflammation
  - ↳ Can complicate autoimmune disease in localized areas (Hashimoto thyroiditis, Sjogren syndrome in the lacrimal glands)
  - ↳ Can complicate Helicobacter pylori-chronic gastritis
- Infiltrates the epithelium and causes its destruction

Remember:

H. pylori is considered an oncogenic organism

Mantle cell lymphoma

- Arises from naïve B-cells in mantle zone [which precedes the B-cell maturation, it's like a reception area before the germinal center]
- **Most commonly in older men**

  - ↳ t(11;14) that fuses cyclin D1 gene to IgH [The same mechanism we talked about before where the genes fusing with IgH gene are highly expressed]
  - › Overexpression of cyclinD1, promotes progression of cell cycle (it activates the G1 phase)

- Commonly arises in lymph nodes and affects them in addition to Waldeyer ring (oral and nasal cavity)
- Commonly involve BM, blood in 20%, sometimes in GIT [it appears as submucosal nodules → lymphomatoid polyposis]

Morphology under the microscope: it looks like follicular lymphoma→ small centrocytes, BUT in diffuse pattern [no follicles]

› Bcl6 and CD10 are -ve because they're not of a follicular origin

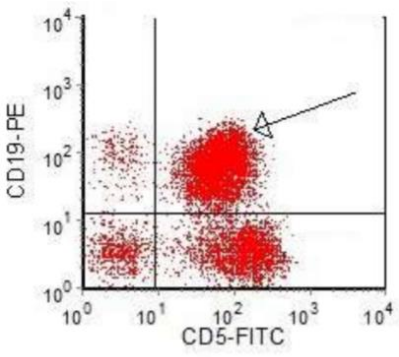
Small lymphocytic lymphoma SLL/CLL

When it arises in and circulates the blood it's called: Chronic lymphocytic leukemia

- Low-grade B-cell neoplasm [Lymphocytic means the cells are Mature]
- Affects **elderly**
- Can arise in LNs and solid tissue (SLL) and represents only 4% of NHL
  - ↳ or in BM and peripheral blood (CLL) and this is the **Most common leukemia in adults**
- Not common in Asia. However, in western countries it is.

❖ pathogenesis:

- 2 pathways:
  - › **Increased Bcl2 protein**, secondary to deletion mutation in genes encoding micro-RNAs that are negative regulators that counteract Bcl2
  - › A surface immunoglobulin called **B-cell receptor (BCR), is autonomously active**, activating a protein called Bruton tyrosine kinase (BTK) that activates genes **promoting cell survival** and long life
- Chromosomal translocation is rare → an exception of the B-lymphomas
- Lymphoma cells express CD20 [B-cell origin] AND Bcl2 and CD5 [which are a clear sign of malignancy since Bcl2 is positively stained in malignant cells and CD5 is a T-cell marker!]



This is a flow cytometry test performed on fluids, [for confirmation of CLL] each spot indicates the presence of a certain marker in the cells, the table below shows the meaning of each spot.

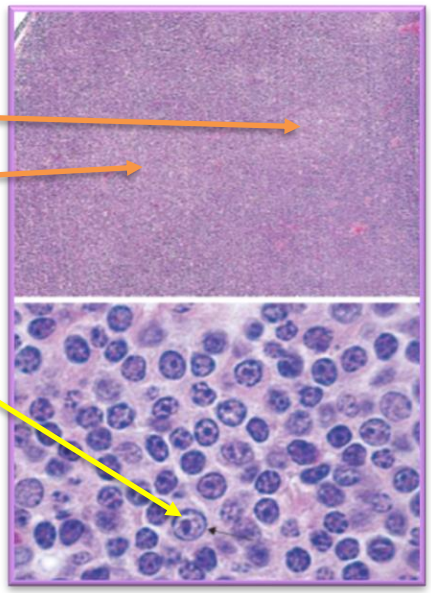
We already know that:

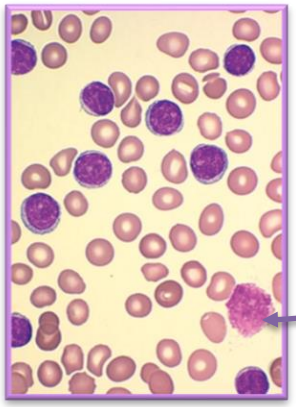
- CD5 is a T-cell marker
- CD19 is a B-cell marker
- BOTH on the same cell means CLL

		CD5 -	CD5 +
CD19	+	B	CLL
	-		T

❖ Morphology in SLL:

- LN shows effacement of architecture [diffuse]
- Proliferation centers: focal pale areas [cells with a lot of cytoplasm] containing large number of prolymphocytes and increased mitosis.
- Most of neoplastic cells are **small** in size, **round, dark chromatin**, along with few large cells with central prominent nucleolus [prolymphocyte] which increase in number as the disease progress.





❖ Morphology of CLL:

- Leukemic cells appear similar to lymphocytes but they're high in number.
- Occasional prolymphocytes
- Smudge cells which are Broken [:'( ] and dead lymphocytes

❖ Clinical features:

- Many patients are asymptomatic [the disease is discovered incidentally through a high lymphocyte count in a CBC test]
- Leukocytosis can reach very high levels (>200,000) [because it's an indolent disease that takes its time]
  - ↳ It is called leukaemia because the blood is FULL of WBCs
- 50% have additional generalized lymphadenopathy and hepatosplenomegaly
- 50% of patients have Immune dysfunction, by suppressing normal B-cells, resulting in hypogammaglobulinemia (decreased Immunoglobulins)

- Anemia: in contrast to the previous point 15% of patients develop auto antibodies by B-cells against RBCs and platelets [causing cold type immune hemolytic anaemia]
    - Thrombocytopenia: attacking platelets causes a condition similar to immune thrombocytopenic purpura [ITP]
- Variable outcome: many patients have similar survival to general population [remember that they're old originally]
    - P53 mutation in some patients makes prognosis worse
- Richter transformation: in 10%, the disease becomes very accelerated with predominance of large cells
    - Very poor prognosis, patients survive <1 year

Precursor B & T cell neoplasms

❖ General info.:

- Precursor neoplastic cells: the most **immature** lymphoid cell [lymphoblast]
    - Lymphoblastic lymphoma: when occurs in solid tissue (T type is more common than B)
    - Acute Lymphoblastic Leukemia(ALL): when circulates peripheral blood and involve bone marrow (B>T), it is aggressive & progresses rapidly.
- **B-ALL is the most common childhood malignancy**
- Aggressive neoplasms, express CD34 [membrane marker] and TDT [nuclear]
- T-ALL is less common, presents in adolescents, arises in the thymus, more common in boys.
- B-ALL tends to disseminate to solid organs (brain, testis, spleen), because the lymphocyte normally circulates the blood then resides in tissues, these do the same.

❖ Pathogenesis:

- Mutations in transcription factors for genes responsible for maturation of blasts
- Mutations in **RAS signaling** and **tyrosine kinase proteins** promoting cell survival
- In T-LL: 70% have mutations in NOTCH1 gene
- In B-LL, mutation is in PAX5 gene {remember B with P}
- Most childhood B-ALL have hyperdiploidy (contains >50 chromosomes) and some have t(12;21) mutation, involving **ETV6 and RUNX1** genes which create a new transcription factor when they fuse.

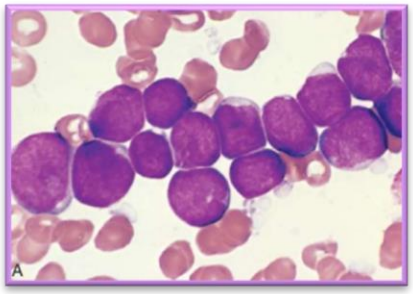
- Adult B-ALL exhibits t(9;22) between **ABL and BCR** genes (Philadelphia chromosome), similar to chronic myeloid leukemia, creating a new **tyrosine kinase protein** coding gene
  - ↳ **Imatinib** is an antibody drug that blocks this tyrosine kinase
- T-ALL shows mutation in PTEN gene (tumor suppressor) and CDKN2A (promotes cell cycle)

> *Interesting info:*
>
> Philadelphia chromosome is the first discovered translocation abnormality in human cancer, and Imatinib is the first targeted therapy used in cancer.

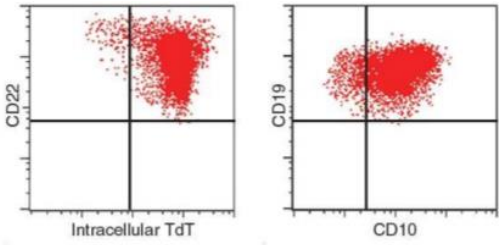
❖ Morphology of ALL:

Blasts are **large** compared to lymphocytes,
With a high Nucleus/Cytoplasm ratio
[The cytoplasm is 💪]

- Chromatin is open [pale] because this cell isn't very active [immature]
- Nucleolus sometimes is present
- Cytoplasm doesn't have granules



flow cytometry confirms if these are lymphoblasts and specifies the type B or T



- CD22 & CD19 are B-cell markers
- CD10 is present in lymphomas of follicular origin and immature cells
- TDT is an immature lymphoblast marker

❖ Clinical features:

- Again, It's an **acute aggressive** disease
- Anemia, thrombocytopenia → secondary to destruction of the bone marrow
- Damage to solid organs secondary to leukemic infiltration
- Prognostic factors in B-ALL:
  - ↳ favorable (good prognosis- they respond to chemo): hyperdiploidy, low WBC count, age between 2-10 years
  - ↳ unfavorable (poor prognosis): age < 2 years, age in adolescents or adults, WBC count >100k

Plasma cell myeloma

Another name: multiple myeloma

- Common neoplasm, arises from malignant plasma cells
- Commonly in **elderly**, more common in men, African origin
- Malignant plasma cells secrete a large amount of Ig that's usually of the same type → monoclonal protein (M protein), most commonly IgG (60%), then IgA (20-25%), followed by other types.
- Sometimes they secrete only light chain in large amounts (kappa or lambda) and that can be detected in urine & is called [Bence Jones proteins]
  - Bence jones proteins +ve → Plasma Cell myeloma

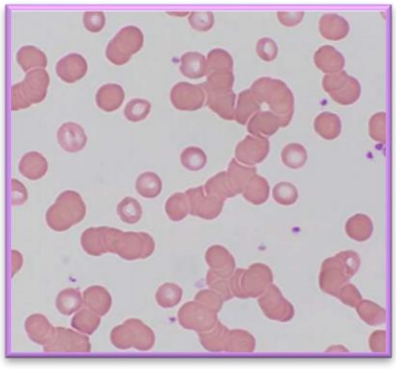
❖ Pathogenesis:

- t(11;14) cyclinD1 or cyclinD3 fusing with IgH gene
  - MYC gene mutation occurs late in disease
- Malignant plasma cells are **biologically very active**; they need IL-6 for survival, which is 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 and erosions.
  - Other products inhibit osteoblast function (hypercalcemia because the calcium gets out of the bone matrix; **pathologic fracture** because of thin bone)
  - Patients have fractures, bone pain and symptoms related to hypercalcemia especially in the heart and the brain, also kidney stones.
- Malignant plasma cells Suppress normal B-cell function [immune suppression]
- Directly inhibits erythropoiesis (early onset anemia) → V.common
- Renal failure: multifactorial:
  - obstruction to distal collecting tubules by (Bence Jones protein, immunoglobulin, albumin) causing proteinaceous cast [material blocking the tubule]
  - Hypercalcemia produces kidney stones, causing further obstruction and renal infection, which is bad because the patient is immunosuppressed, and it could worsen the anaemia, because there'll be decreased production of erythropoietin, this can be fatal.

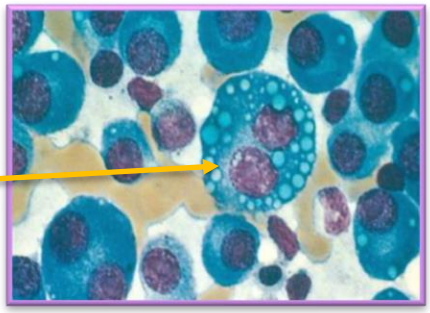
❖ Morphology:

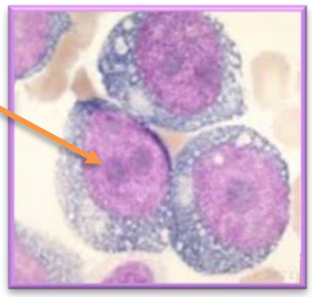
- In Peripheral blood: characteristically RBCs show rouleaux formation
  - Immunoglobulins bind multiple RBCs together

[this is different from agglutination of cold type IHA]



- BM: we observe an increased number of plasma cells (>10% of bone marrow cells need to be plasma cells for diagnosis to be made)
- Some Abnormal figures with multinuclei and cytoplasmic **vacules containing Igs** can also be observed
- Sometimes we can observe prominent nucleoli instead of the normal cartwheel chromatin appearance of plasma cells' nuclei



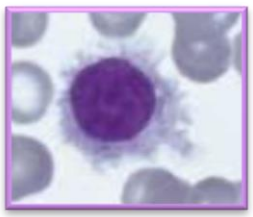


❖ Clinical and laboratory findings:

- Very high Erythrocyte sedimentation rate
- CRAB (hypercalcemia, renal failure, anemia, bone fracture→ many lytic lesions)
- Amyloidosis: occurs in few patients, secondary to deposition of light chain K or lambda in the form of [AL-amyloid] →which causes secondary conditions depending on the site.
- In advanced disease: pancytopenia [due to destruction of BM], plasma cell leukemia & visceral damage
- Slowly growing, which is why they're NOT curable with conventional chemotherapy. Instead, we give other agents called immune modulators.
  - **Lenalidomide:** [Drug] which inhibits oncogenic proteins
  - Proteasome inhibitors: [Drugs] which inhibit degradation of misfolded proteins → accumulation → cause apoptosis in plasma cells

Hairy cell leukaemia

❖ General information:



- Uncommon low-grade B-cell leukemia
- Affects older patients, more common in men, smokers
- Characteristic: Leukemic cells are few in number, have prominent cytoplasmic projections [hair]
- Leukemic cells heavily infiltrate BM and spleen→ pancytopenia, Splenomegaly
- Leukemic cells are biologically active; they **inhibit hematopoiesis** [that's why patients present with pancytopenia early on] and **cause bone marrow fibrosis**
  - Sometimes it looks like aplastic anaemia → empty BM, very few cells.
- Affects BM and spleen, LN involvement is very rare
- Mutation in serine/threonine kinase BRAF gene [found in solid tumors]
- Very sensitive to chemotherapy

peripheral T-cell lymphoma

Most common mature T-cell lymphoma

- Aggressive, poor prognosis [T-cell lymphomas are generally aggressive :'(]
- Simple diagnosis by exclusion of T-lymphoblastic or cutaneous lymphoma
- Neoplastic cells secrete inflammatory cytokines like normal cells, causing severe inflammation even when the tumor is small
- Express T-cell markers: CD2, CD3, CD5, CD7 and are negative for TDT [because they're mature]

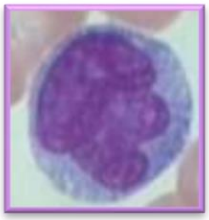
Cutaneous lymphoma

Mycosis fungoides and Sezary syndrome

Because it grows like a mushroom

This is a subtype of it that's leukaemic

- **Most common cutaneous lymphoma**
- Neoplastic CD4+ T-cells, that home to skin
- Patients present with a long history of **erythema**, which progresses to **plaque** then **tumor**
- Shape characteristics: Neoplastic lymphocytes have irregular nuclear membrane [cerebriform]
- Infiltrate epidermis and dermis, but most commonly it happens at the junction between them.
- With disease progression, lymphoma disseminates to LNs and viscera
- Sezary syndrome: a variant of MF. From the beginning, patients present with widespread erythema and we see these cells in the skin, but they also have blood leukemia of neoplastic cells in which they're called [Sezary cells]

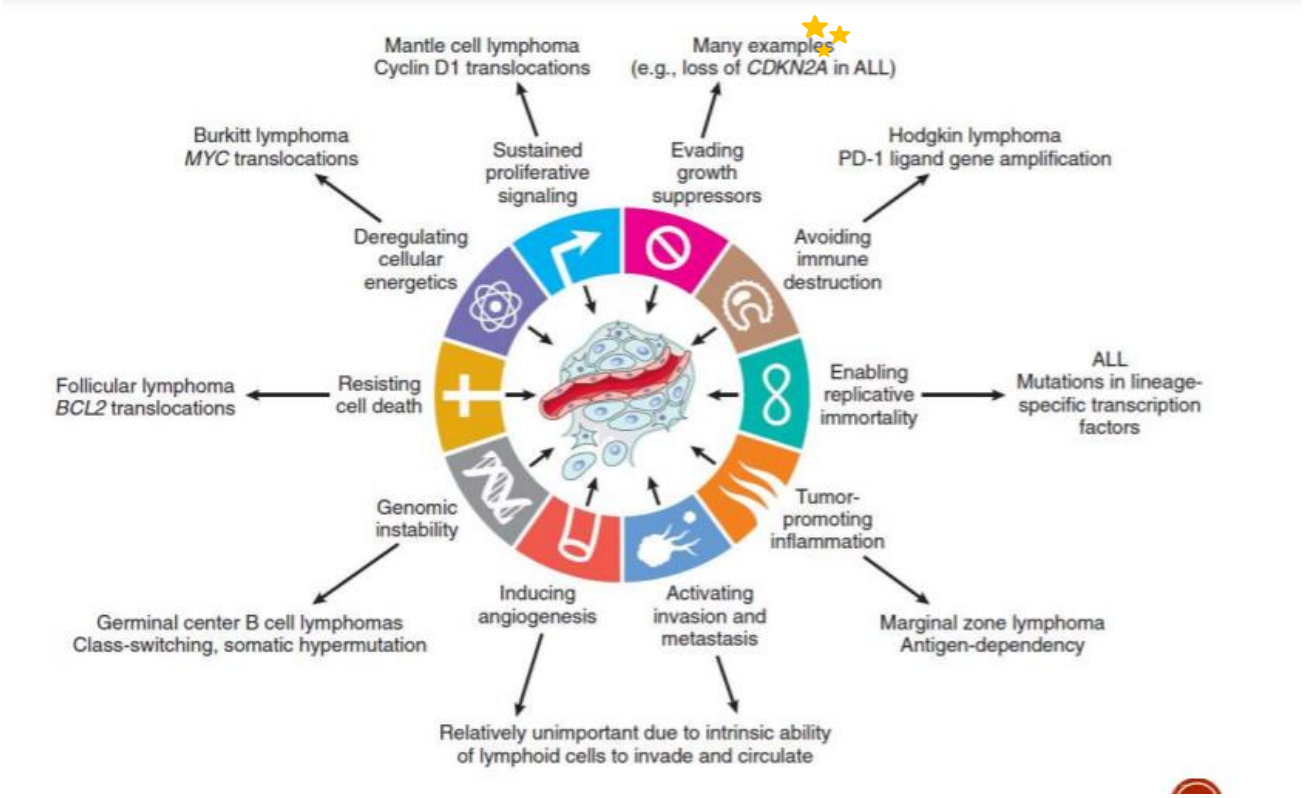


Adult T-cell Leukemia/ lymphoma

- Neoplastic CD4+ T-lymphocyte
  Caused by a retrovirus; human T-cell leukemia virus1 (HTLV-1)
- **Rare in our region** but Endemic in Japan, Caribbean basin, West Africa and some parts of South America
- Sporadic everywhere

- Virus is similar to HIV: transmitted through body fluids (blood, breastfeeding, sexual intercourse)
- 5% of virus carriers develop neoplasm, after a latent period of 40-60 years.
- Mechanism: Tax protein, which is essential for viral mRNA transcription, also causes proliferation of the cell through the following pathways: PI3 kinase and cyclin D1, 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
- Characteristically: Neoplastic cells express CD25 (IL-2 receptor)
- Poor prognosis

This scheme shows all the mutations in lymphomas in general:



Good Luck