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Pathology HLS

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PATHOLOGY OF BLOOD AND LYMPHATIC SYSTEM-8

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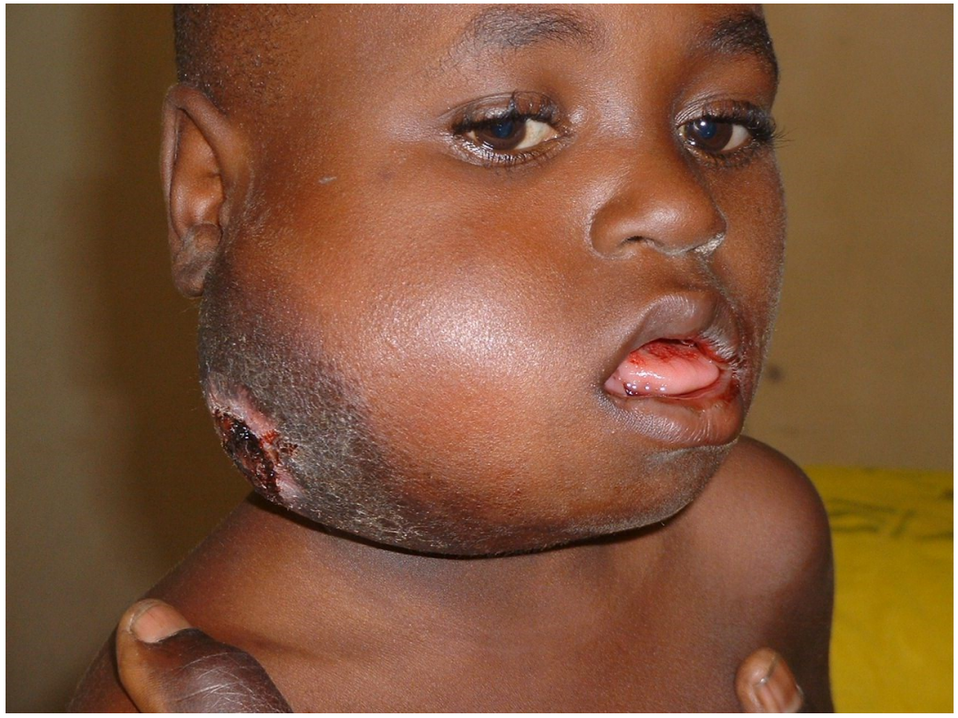
BURKITT LYMPHOMA

- Most common NHL in children (remember that the most common lymphoma in children is Hodgkin's, so Burkitt's is the second most common lymphoma in children and it is the most common NHL)

- Three types:

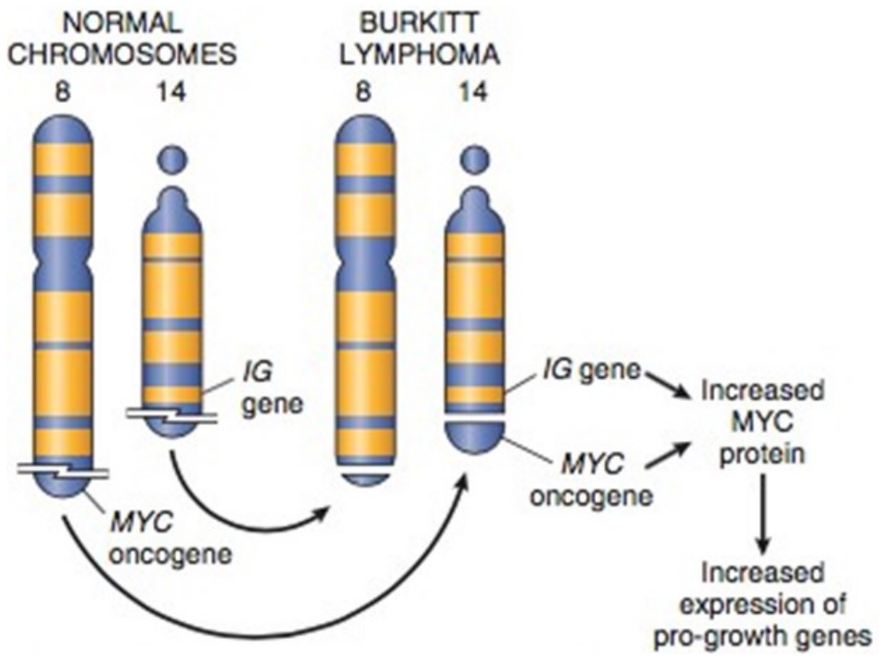
1. Endemic in parts of Africa (100% EBV +) (the tumor was first described in Africa by Dr. Denis Parsons Burkitt, the endemic variant of Burkitt lymphoma is always positive for Epstein-Barr virus antigens)
2. Sporadic in the rest of the world (20% EBV +), latent infection (less association with EBV than the endemic variant, and usually results from a latent infection with EBV)
3. Immunodeficiency associated BL (arises in the presence of HIV (AIDS) and other immunodeficiencies)

- What is peculiar about Burkitt lymphoma is that it is primarily an Extranodal disease: jaw (the most common site for the endemic variant, it causes jaw enlargement and severe disfigurement of the face), terminal ileum, retroperitoneum, ovary, CNS (sporadic), sometimes leukemic (arising in the bone marrow or peripheral blood).



PATHOGENESIS

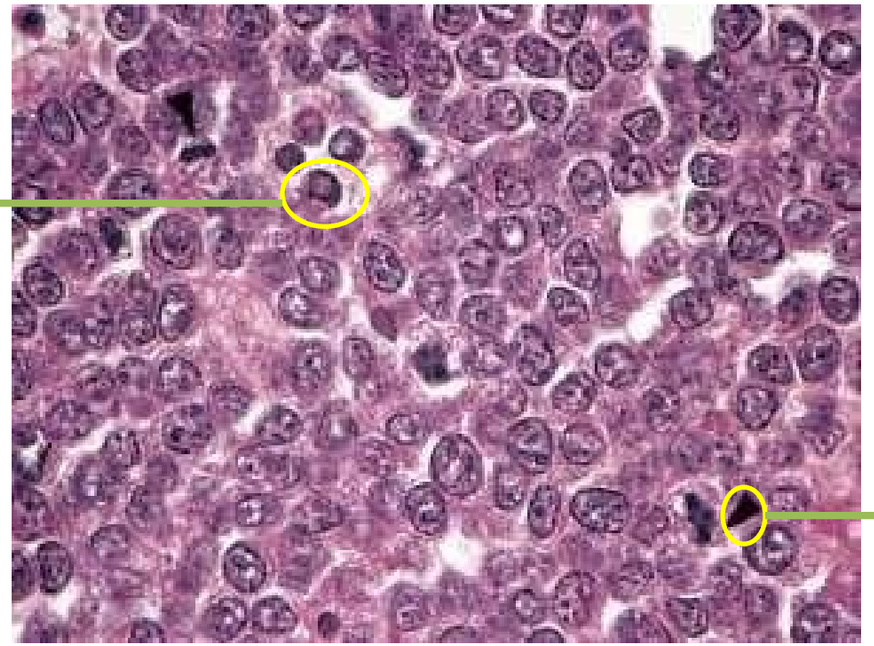
- t(8;14) MYC → IgH (MYC gene is present on chromosome 8, in Burkitt lymphoma, this MYC gene is translocated to chromosome 14 next to the immunoglobulin heavy chain gene, which is a very active gene in B cells, so when you put MYC gene, which is a modulator of Warburg metabolism, next to it, that makes the MYC gene over activated, and thus cancer occurs.)
- Warburg metabolism is an alternative of normal aerobic glycolysis, this type of metabolism occurs only in fetal tissues, and it is a hallmark of cancer cells. In this type of metabolism, sources of energy are not degraded completely, and carbon is preserved and is not completely oxidized to CO_2 (this favors the anabolic status of the cell) , which promotes cell proliferation and makes cells resistant to hypoxia.
- Overexpression of MYC transcription factor, potent regulator of Warburg metabolism (aerobic glycolysis)
- Neoplastic lymphocytes are B-cells of germinal center origin so they express CD20 (which is specific for B cells) Bcl6, and CD10 (which is specific for germinal center B cells).
- Aggressive, but responsive to chemotherapy



MORPHOLOGY

- Intermediate size cells (this is what makes Burkitt's lymphoma unique among other non-Hodgkin's lymphomas, in which cells are either small or large)
- Monomorphic (meaning that cells are similar to each other)
- Round or oval nuclei (remember that in follicular lymphoma and diffuse large B cell lymphoma, the nuclei were irregular in shape), multiple small nucleoli
- Lipid vacuoles in cytoplasm (we see these vacuoles in the leukemic phase specifically [in fluid preparations])
- Very high mitosis (Burkitt lymphoma is the fastest growing human cancer, the size of the tumor duplicates every 8 hours!!!), tangible body macrophages engulfing nuclear debris (this is because the tumor is characterized by a lot of apoptosis, which attracts macrophages to engulf apoptosomes (nuclear debris), so we call them tangible body macrophages)

This is a tangible body macrophage, notice that it is pale but it contains dark nuclear debris.

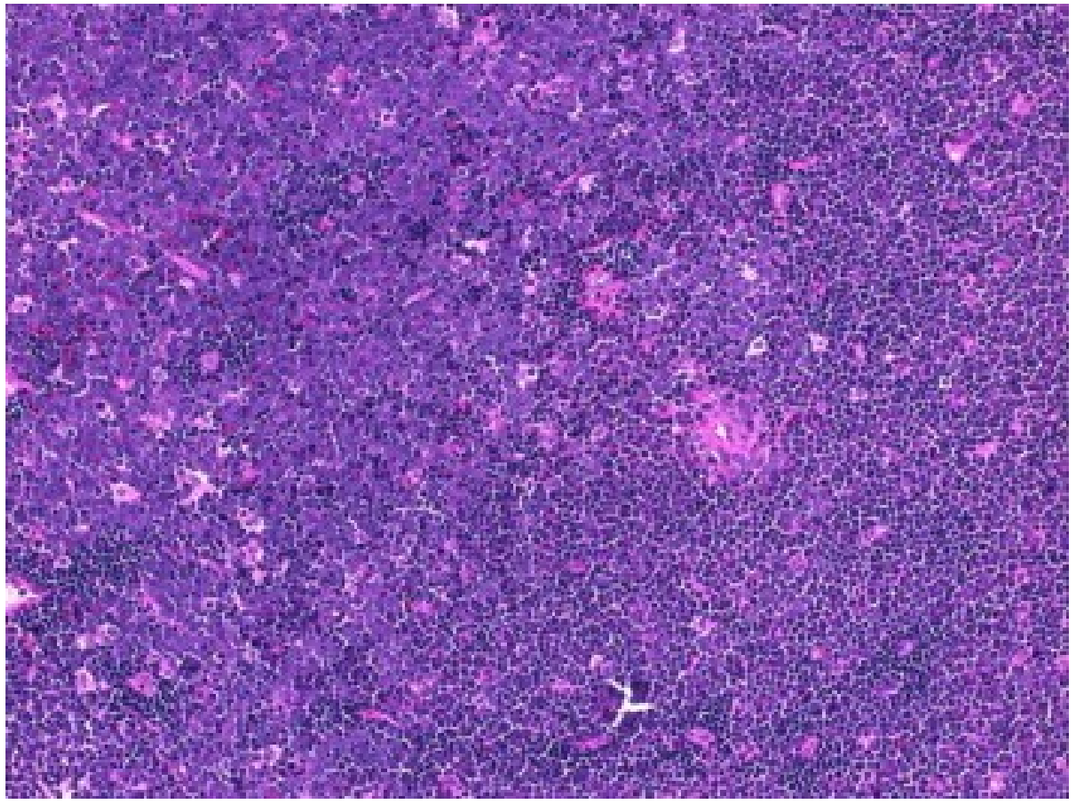


The cells are monomorphic and intermediate in size, the nuclei are round with multiple small nucleoli (the black dots)

This arrowhead indicates mitotic figures

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

The micrograph in the previous slide was at high-magnification, if you examine the tumor under low magnification, you'd notice that it has a characteristic appearance known as starry sky appearance, where the tangible body macrophages appearing as the stars because they are pale on a background of dark neoplastic cells.



Starry sky appearance of Burkitt lymphoma

Van Gogh's starry night

Isn't pathology fascinating ?? 😍

EXTRANODAL MARGINAL ZONE LYMPHOMA

- Predominantly arise outside lymph nodes
- The marginal zone comes after the germinal center, it is the area surrounding the germinal center.
- Because this lymphoma arises in the marginal zone rather than the germinal center, cells appear more mature, they are at the level of maturation just before plasma cells.
- Indolent B-cell lymphoma (the cells are malignant B-cells, but of low grade)
- Second most common lymphoma in extranodal sites in adults (the first being diffuse large B cell lymphoma)
- What's peculiar about this lymphoma is that it Arises in the setting of chronic inflammation
- Can complicate autoimmune disease in localized areas (Hashimoto thyroiditis (it arises in the thyroid), Sjogren syndrome (it arises in salivary or lacrimal glands))
- Can complicate Helicobacter pylori-chronic gastritis (the stomach is the most important site of extranodal marginal zone B-cell lymphoma & H. pylori is a potent oncogenic microbe, as it can cause gastric adenocarcinoma and extranodal marginal zone B cell lymphoma)
- Infiltrate the epithelium (of either the stomach, thyroid, etc.) and causes destruction

MANTLE CELL LYMPHOMA

- Arises from naïve B-cells in mantle zone (the mantle zone is the area between the germinal center and the marginal zone, it precedes the maturation of B cells in the germinal center, once B lymphocytes reach the lymph nodes, they reside in the mantle area)
- Most commonly in older men
- t(11;14) that fuses cyclin D1 gene to IgH locus (As you might have noticed, chromosome 14 is commonly involved in translocations of lymphomas, because it contains the IgH gene, chromosome 11 contains cyclin D1 gene)
- Overexpression of cyclin D1, promote progression of cell cycle (specifically, this cyclin promotes conversion from the G1 phase (growth phase) of the cell cycle to the S phase (DNA synthesis phase).
- Affects LNs, Waldeyer ring
- Commonly involve BM, blood in 20%, sometimes in GIT, appears as multiple submucosal nodules, causing a condition known as lymphomatoid polyposis. In this conditions, polyps appear like adenomas (epithelial growths), but actually they are composed of lymphoid growth.
- Morphology: small centrocytes (just like those of follicular lymphoma, remember that centrocytes are small irregular cleaved cells), but in diffuse pattern (this is in contrast to follicular lymphoma where cells form follicles)
- Also, cells of mantle cell lymphoma are negative for CD10 and Bcl6, because they are not of follicular origin

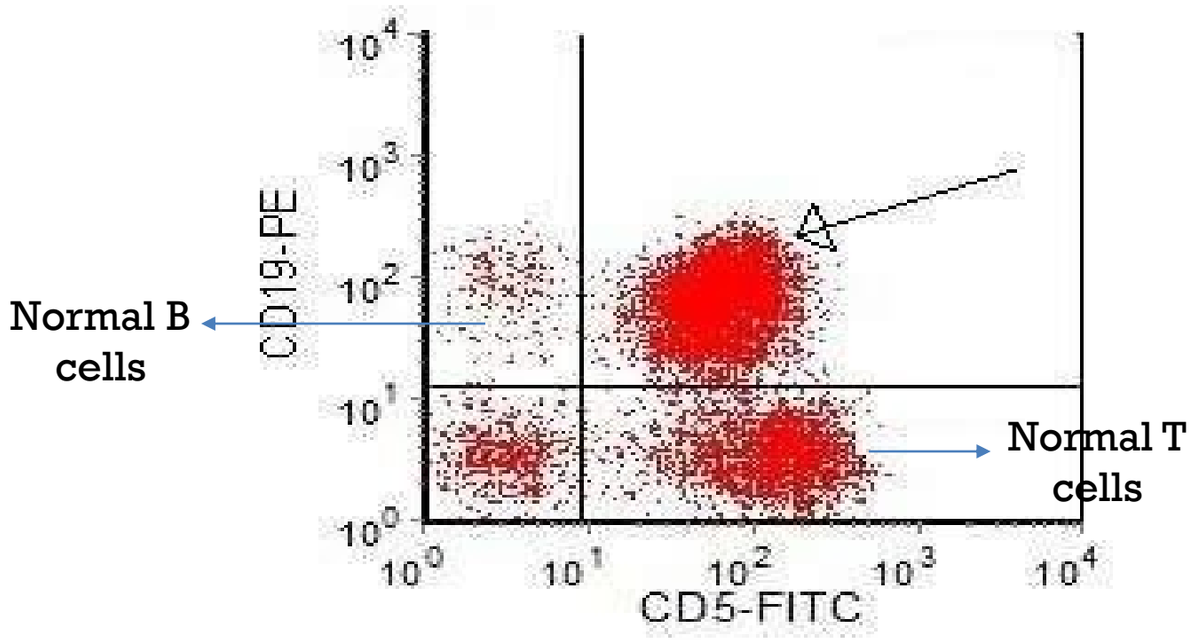
Small lymphocytic lymphoma/chronic lymphocytic leukemia

- A single disease with two faces !!!, when it arises in lymph nodes we call it small lymphocytic lymphoma, but when it arises in the bone marrow and the cancerous cell circulate in the blood, we call it chronic lymphocytic leukemia, it is more common for this disease to arise as a leukemia rather than a lymphoma.
- Low-grade B-cell neoplasm
- Affects elderly
- Can arise in LNs and solid tissue (SLL), or in BM and peripheral blood (CLL)
- CLL is most common leukemia in adults, while SLL represents only 4 % of NHL
- Not common in Asia, but common in the western world and in Jordan.
- Pay attention to the fact that we call it a "lymphocytic" leukemia, meaning that the cancerous cells are mature lymphocytes, however, in acute lymphoblastic leukemia, the cells are immature lymphoblasts.

PATHOGENESIS

- Increased Bcl2 protein, secondary to deletion mutation in genes encoding micro-RNAs that are negative regulators of Bcl2
- Involved in the pathogenesis of this cancer is A mutant surface immunoglobulin called B-cell receptor (BCR), it's autonomously active, activating an intermediary called Bruton tyrosine kinase (BTK) that activates genes promoting cell survival
- Chromosomal translocation is rare (an exception of B-cell lymphomas, where chromosomal translocations are generally common)
- Lymphoma cells express CD20 (as most B-cell lymphomas), Bcl2 (involved in pathogenesis) and CD5 (a marker for T-cell lymphomas, its expression here is aberrant).

as the arrow indicates, there is an expression of both CD5 (a T-cell marker) and CD19 (a B-cell marker) on the same cell, characteristic for CLL/ SLL

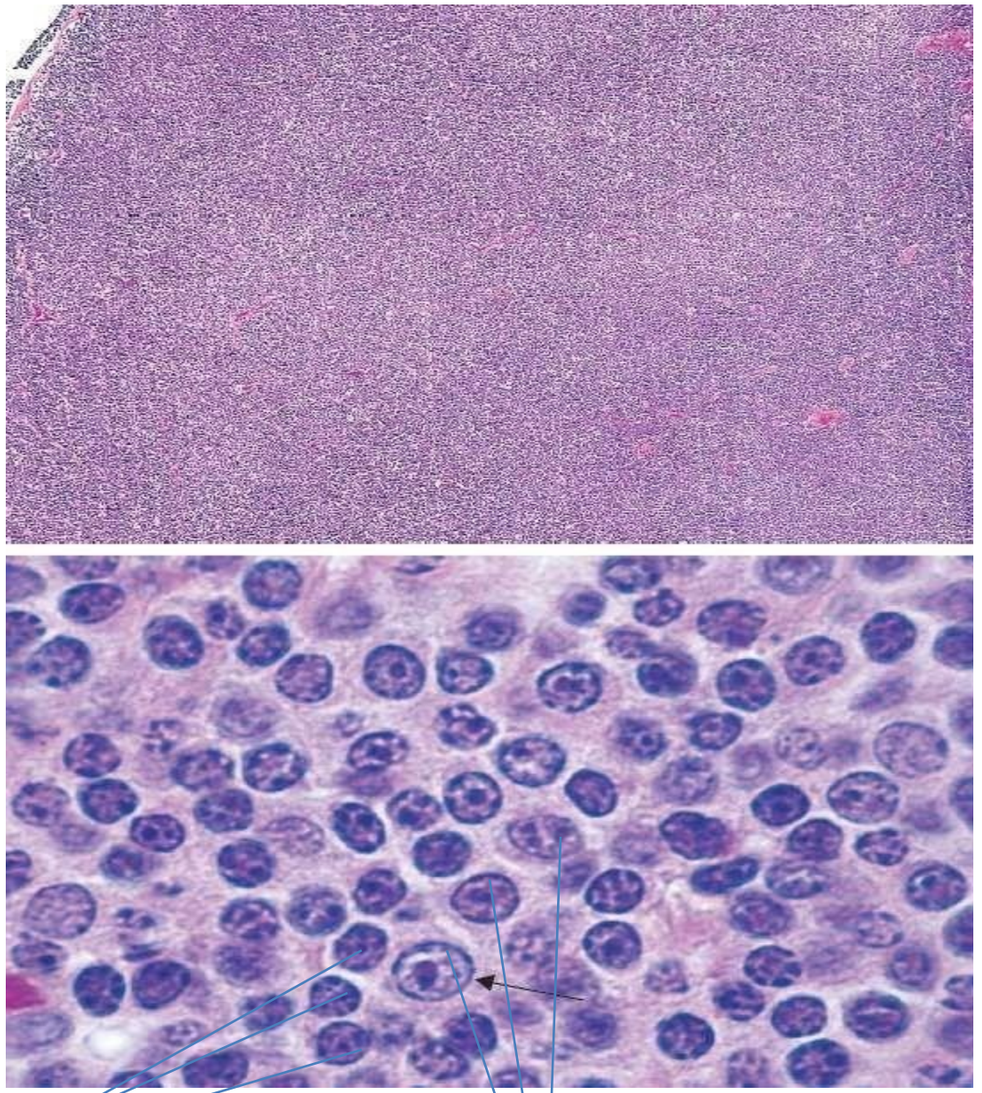


Flow cytometry showing patterns of expression of CD19 and CD5.

Note: flow cytometry is done to examine the patterns of protein expressions for fluid specimens, like blood and bone marrow aspirates, but to know the pattern of expression of proteins in tissue specimens, we use immunohistochemistry.

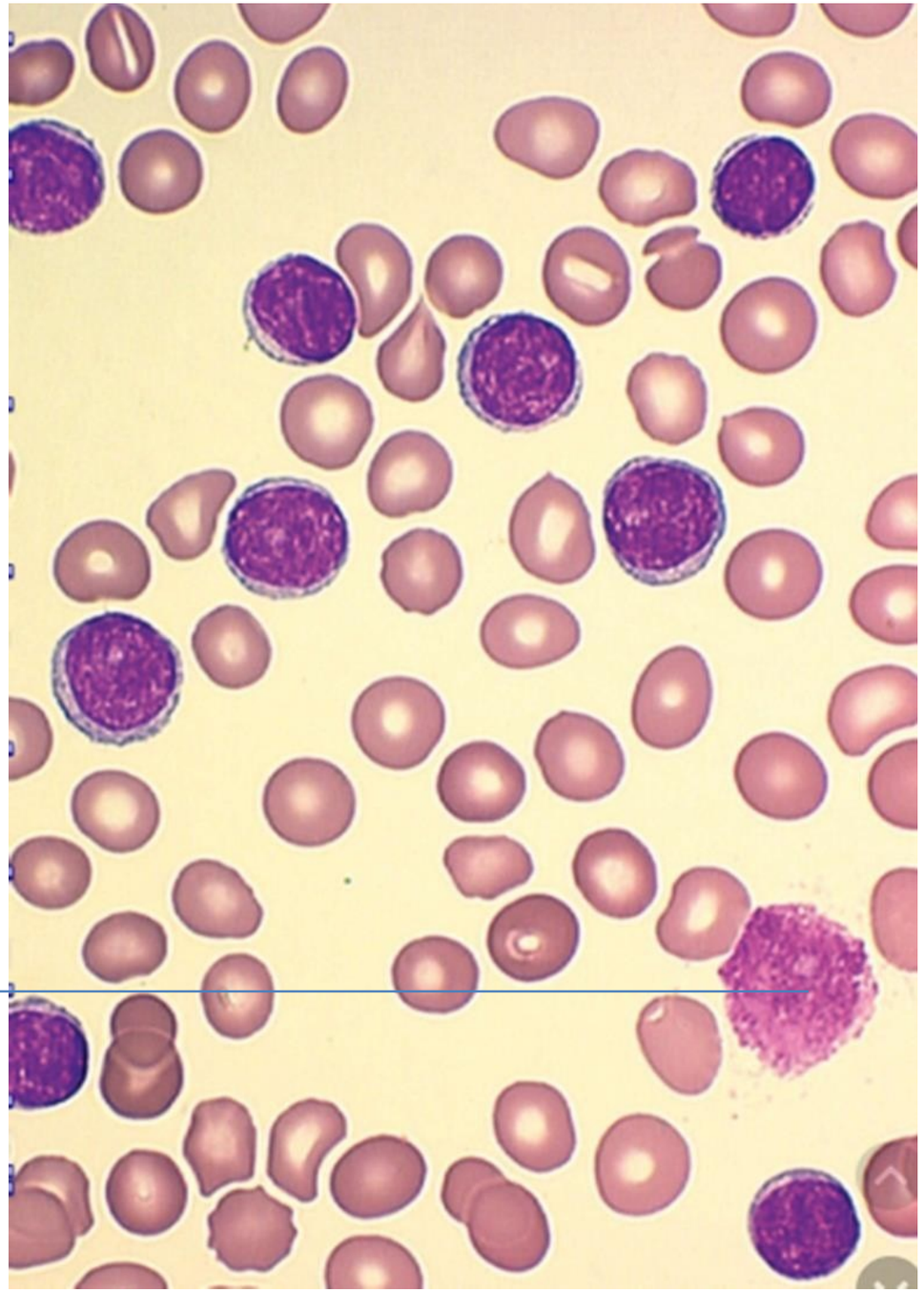
MORPHOLOGY OF SLL

- LN shows effacement of architecture (it appears as a diffuse growth, there's effacement طمس of the architecture, we see no cortex, medulla, follicles, etc.)
- Proliferation centers: focal areas containing large number of prolymphocytes and increased mitosis , these appear as pale areas as you can see in the figure above, these are the areas with the highest mitotic activity, so they have larger cytoplasm and nuclei, that's why this area is pale.
- on higher magnifications, we see that we have two populations of cells: most of neoplastic cells are small in size, round, dark chromatin (lymphocytes), along with few large cells with central prominent nucleolus (prolymphocyte).
- the lymphocytes are the predominant cells in the early disease, but as the disease progresses, more prolymphocytes appear.



MORPHOLOGY OF CLL

- Leukemic cells appear similar to lymphocytes, but they are very high in number.
- Occasional prolymphocytes (which are, as we said, larger cells with prominent nucleoli)
- Smudge cells (which are dead lymphocytes. These cells appear because lymphocytes are very fragile, so they can easily break up when they hit each other, and they do that frequently due to their high number in this disease, resulting in the appearance of these dead figures.



CLINICAL FEATURES

- Remember that the disease affects the elderly, never children or young adults.
- Many patients are asymptomatic, the disease is usually discovered accidentally on a regular complete blood count, were we see a complete blood count.
- Leukocytosis can reach very high levels (>200,000) because it is an indolent low grade disease, leukocytosis can be high enough to make blood appear white !! Therefore, it was called leukemia.
- 50% have generalized lymphadenopathy and hepatosplenomegaly
- Immune dysfunction (immune suppression) is common, by suppressing normal B-cells, resulting in hypogammaglobulinemia where the normal level of antibodies in the blood is decreased (50% of patients)
- Anemia : In contrast, 15% of patients develop autoantibodies against RBCs and platelets causing cold type immune hemolytic anemia, these autoantibodies are secreted by normal B-cells
- Sometimes autoantibodies against platelets are formed, causing Thrombocytopenia: a syndrome similar to immune thrombocytopenic purpura
- Variable outcome: many patients have similar survival to general population, remember that this disease affects the elderly, so it is more likely for them to die from other diseases rather than CLL, In contrast, P53 mutation makes prognosis worse
- In 10% of patients, the disease becomes very accelerated, we call that setting Richter transformation, in which we have predominance of large cells, patients survive <1 year, so if Richter transformation occurs, the prognosis is very poor.

PRECURSOR B AND T CELL NEOPLASMS

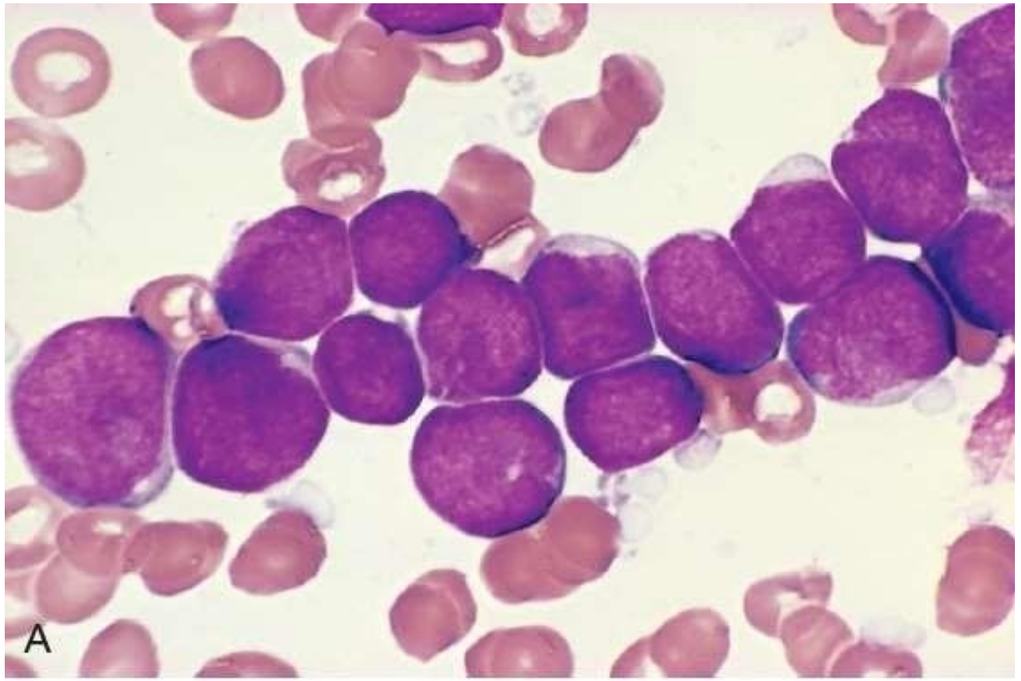
- A precursor means the most immature cells, these are known as lymphoblasts, so neoplasms of precursor cells are known as lymphoblastic leukemias or lymphomas.
- Lymphoblastic lymphoma when occurs in solid tissue (like lymph nodes) (T cell neoplasms are more common in this context)
- Acute lymphoblastic leukemia when circulates peripheral blood and involve bone marrow (B cell neoplasms are more common in this context)
- An important difference between acute lymphoblastic leukemia and chronic lymphocytic leukemia (CLL) is that ALL is present in acute and rapid symptoms, and it is an extremely aggressive disease in which the patient might die in weeks if not treated, this is in contrast to CLL where many patients are asymptomatic. Also, in ALL the neoplastic cells are immature lymphoblasts, so they behave in an aggressive way, in contrast to CLL where the cells are mostly mature lymphocytes.
- B-ALL is the most common childhood malignancy (including all types of cancer).
- Neoplastic cells are lymphoblasts, the most immature lymphoid cell. Aggressive neoplasms, express CD34 (a membranous protein) and TDT (Terminal deoxynucleotidyl transferase, a nuclear protein).
- T-ALL is less common, presents in adolescents, involving thymus (the largest reservoir of T lymphoblasts in the body), more common in boys
- B-ALL tends to disseminate to solid organs (brain, testis, spleen) (because the neoplastic cells are able to mimic the behavior of normal lymphoblasts, which usually circulate in the blood and reside in tissues).

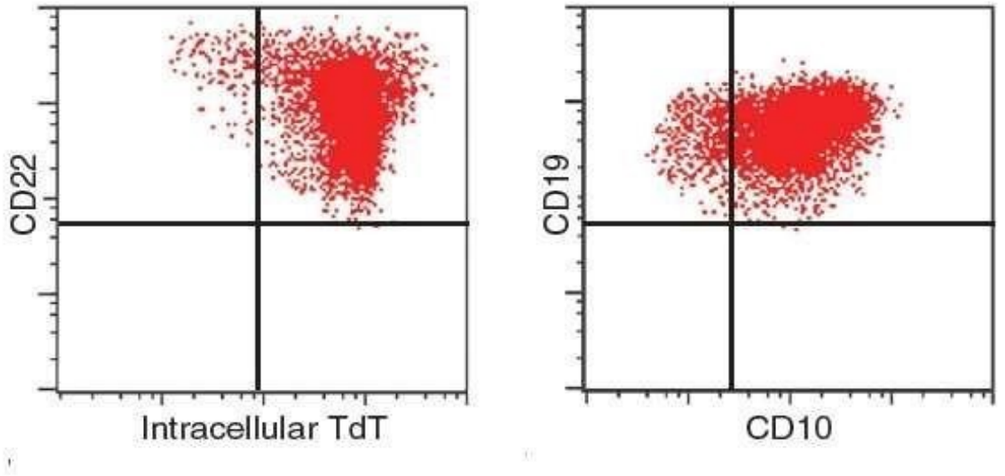
PATHOGENESIS

- Mutations in transcription factors for genes responsible for maturation of blasts, so the maturation of the blasts is blocked.
- Note that all these mutations have a diagnostic value, we can look for these mutations using molecular techniques to confirm a diagnosis.
- In T-LL: 70% have mutations in NOTCH1 gene which is a transcription factor involved in maturation.
- In B-LL, mutation in PAX5 gene which is also a transcription factor involved in maturation.
- Mutations in RAS signaling and tyrosine kinase proteins promoting cell survival are also involved in the pathogenesis.
- Most childhood B-ALL have hyperdiploidy (meaning that the lymphoblasts abnormally contains >50 chromosomes) and t(12;21), a translocation involving ETV6 and RUNX1 genes, these two gene fuse in this translocation, creating a new transcription factor.
- Adult B-ALL exhibits t(9;22) between ABL and BCR genes, these two genes fuse forming what is known as Philadelphia chromosome, which is also formed in chronic myeloid leukemia, creating a new tyrosine kinase protein , this potent tyrosine kinase allows the cell to survive indefinitely. This translocation was the first chromosomal abnormality detected in human cancer.
- Imatinib is a pioneer drug approved for treatment of adult B-ALL, this drug is basically an antibody that is targeted against the mutant tyrosine kinase which is produced in adult B-ALL and chronic myeloid leukemia, this drug was the first targeted therapy drug approved for a human cancer. Targeted therapy means drugs that are targeted against mutant proteins, it is usually specific, in other words, each drug only works against a certain cancer, unlike chemotherapy which is not specific and targets DNA synthesis, so it kills all rapidly dividing cells.
- T-ALL shows mutation in PTEN gene (tumor suppressor) and CDKN2A (promotes cell cycle).
- Despite that we mentioned all these mutations, acute lymphoblastic leukemia is still considered a simple neoplasm, where the number of mutations does not exceed 10.

MORPHOLOGY OF ACUTE LYMPHOBLASTIC LEUKEMIA

- lymphoblasts are large compared to lymphocytes, with high N/C ratio (the nucleus occupies most of the cell volume) (compare their size to RBCs, knowing that the normal lymphocytes is only a little bit larger than RBCs).
- Chromatin is open (pale) (because the cells are immature)
- Nucleolus sometimes present
- Cytoplasm is not granular (in contrast to myeloblasts which are the cells of acute myelogenous leukemia)
- Flow cytometry is important in diagnosis, it confirms that these are lymphoblasts not lymphocytes, and it differentiates T-ALL from B-ALL.
- In the left figure, the cells are positive for CD22 (as most B-cell neoplasm) and TDT (as most immature lymphoid neoplasms) (remember that CD34, CD10, TDT are markers for lymphoblasts)
- In the right figure, the cells are positive for CD19 (as most B cell neoplasms) and CD10 (which is a marker for lymphoblasts and lymphocytes of follicular origin)





CLINICAL FEATURES OF ACUTE LYMPHOBLASTIC LEUKEMIA

- Anemia, thrombocytopenia, those are secondary to the destruction of the bone marrow by neoplastic cells, just like myelophthisic anemia.
- Damage to solid organs secondary to leukemic infiltration (here, the symptoms will be related to the organ involved, imagine if the cells invade the brain !!!)
- Favorable prognostic factors in B-ALL (patients with these factors respond well to chemotherapy): hyperdiploidy, low WBC count in the peripheral blood, age between 2-10 years
- Poor prognostic factors in B-ALL: age < 2 years, age in adolescents or adults (in which the ABL-BCR mutation has occurred) ,WBC count >100k

PLASMA CELL MYELOMA (MULTIPLE MYELOMA)

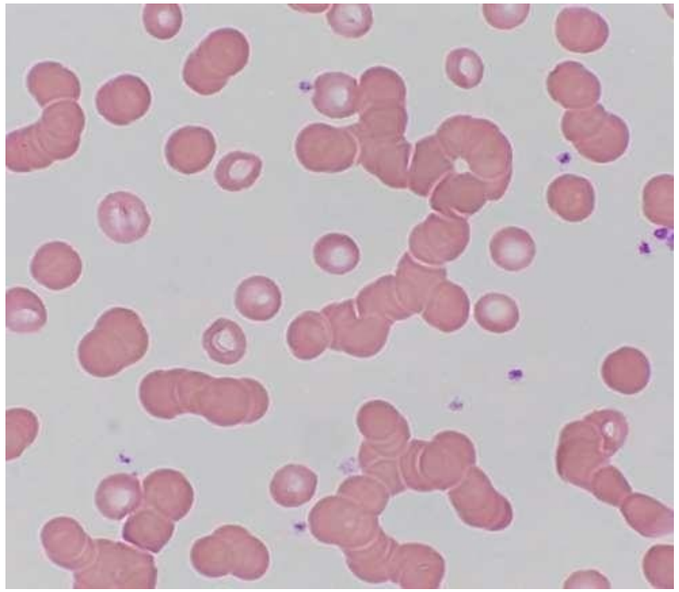
- Common neoplasm (constitutes 10% of bone marrow neoplasms)
- Arises from plasma cells, which the most mature B cells, they express CD134
- Common neoplasm
- Commonly in elderly, more common in men, African origin
- Malignant plasma cells secrete a large amount of immunoglobulins, and because, as any cancer, the tumor arises from a single cell (clonality), all cells of the tumor secrete the same immunoglobulin in type and specificity, this is known as monoclonal protein (M protein), most commonly IgG (60%), then IgA (20-25%), followed by other types.
- the antibodies (immunoglobulins) secreted by neoplastic cells in this tumor are monoclonal, elevation antibodies in the blood that are monoclonal (detection of a large amount of a single type of immunoglobulin) is characteristic for this cancer.
- Sometimes, the malignant plasma cells do not secrete a full immunoglobulin, instead they might secrete only light chain (kappa or lambda) (remember that an antibody is formed from two light chains and two heavy chains), these light chains can be detected in urine, we call them Bence Jones proteins. Detection of these proteins in urine is characteristic for multiple myeloma.

PATHOGENESIS OF MULTIPLE MYELOMA.

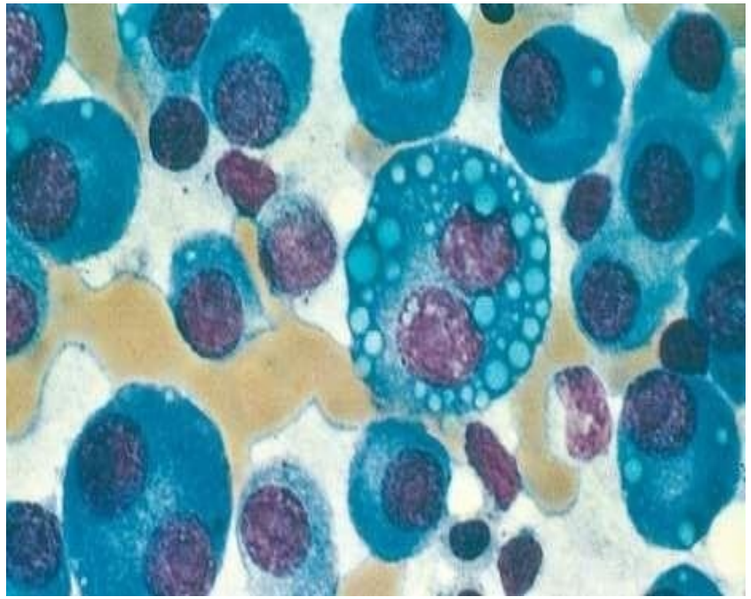
- t(11;14) IgH-cyclinD1 and cyclinD3 (similar to that of mantle cell lymphoma, Cyclin D1 or Cyclin D3 genes which are cell cycle activators fuse with the immunoglobulin heavy gene, making them very active, but remember that this is a different neoplasm, so there are other mutations involved).
- MYC gene mutation is a common finding, but it occurs late in disease (the same mutated gene of Burkitt lymphoma)
- IL-6 is important is plasma cell survival, in the case of multiple myeloma, IL-6 is secreted in high amounts from BM stroma, including 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 fractures) (therefore, the disease is called multiple myeloma, because bones are destroyed in multiple sites in the body), patients with multiple myeloma commonly present with bone pain and symptoms related to hypercalcemia, including arrythmias, neurological symptoms, kidney stones, etc.
- Malignant cells also cause Suppression of normal B-cell function, so patients are immunocompromised.
- Malignant cells also Directly inhibit erythropoiesis, so early onset anemia is very common in patients with multiple myeloma.
- Renal failure is common, occurs due to multiple factors in multiple myeloma, and it can be fatal: it occurs due to physical obstruction of distal collecting tubules by proteinaceous cast composed of Bence Jones protein, immunoglobulin, albumin.
- Hypercalcemia produces kidney stones, causing further obstruction and renal infection (renal infection occurs due to obstruction of urine which allows bacteria to grow, in addition to the state of immunosuppression that the patient has, this obstruction may result in pyelonephritis, urosepsis and death).
- Renal failure worsens the anemia due to loss of erythropoietin.

MORPHOLOGY OF MULTIPLE MYELOMA

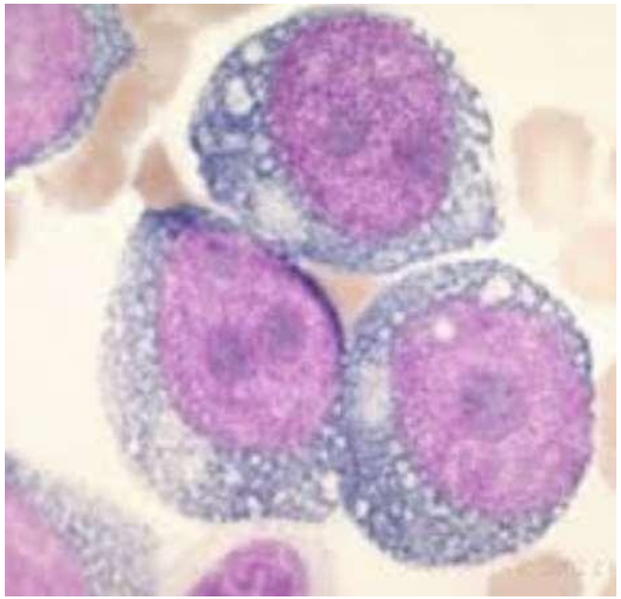
- Peripheral blood: RBCs show rouleaux formation, this occurs because immunoglobulins bind RBCs in a line behind each other, plasma cells are rarely detected in peripheral blood as they mostly reside in the bone marrow.
- BM: increased number of plasma cells (>10% of bone marrow cells), these plasma cells contain abnormal mitotic figures. Also, normally, plasma cells are very rare, and they never exceed 2% of bone marrow cells. In multiple myeloma, plasma cell percentage in the bone marrow might exceed 30%, but we need only 10% to confirm a diagnosis.
- Morphologically might resemble normal plasma cells, or become abnormal (prominent nucleoli, multinucleation, cytoplasmic vacuoles that contain immunoglobulins)



Peripheral blood, notice the rouleaux formation

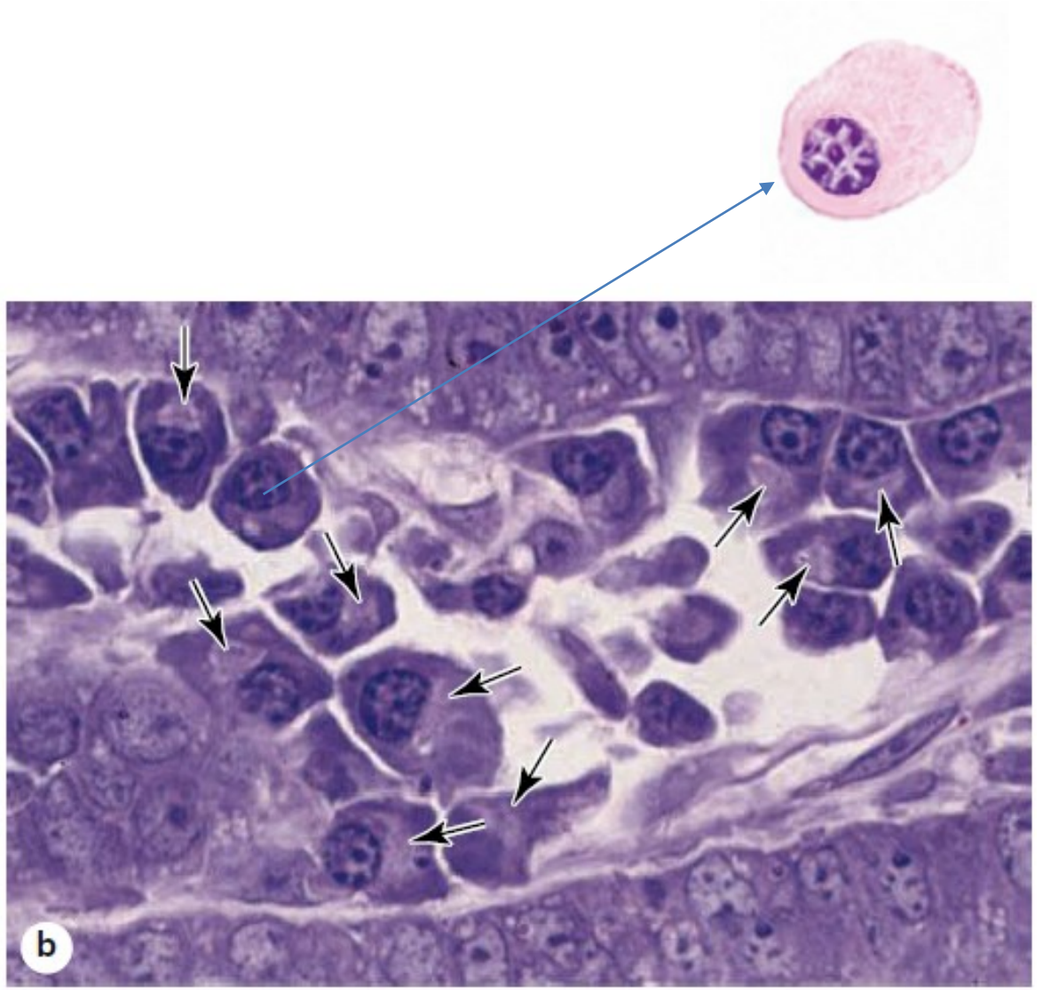


Bone marrow aspirate, notice that some plasma cells contain two nuclei (which is abnormal) and cytoplasmic vacuoles



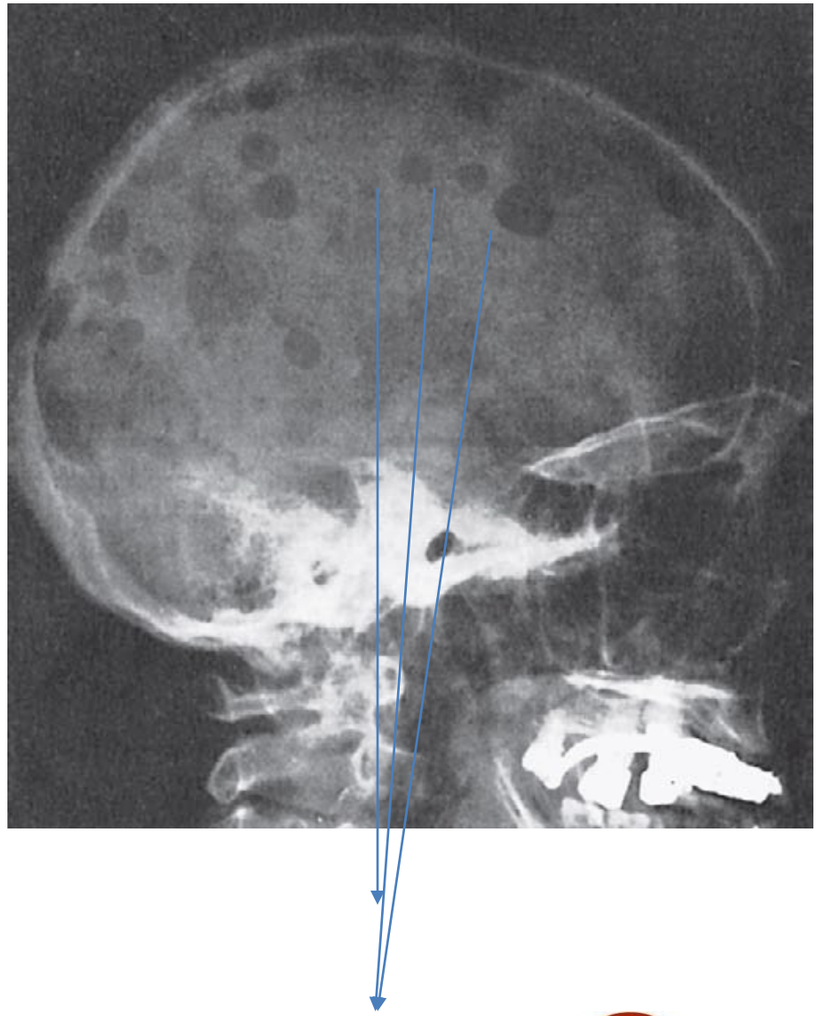
Notice the nucleoli.

Note: normal plasma cells have a special appearance of their nucleus called cartwheel or clockface appearance, this appearance is lost in multiple myeloma.



CLINICAL AND LABORATORY FINDINGS OF MM

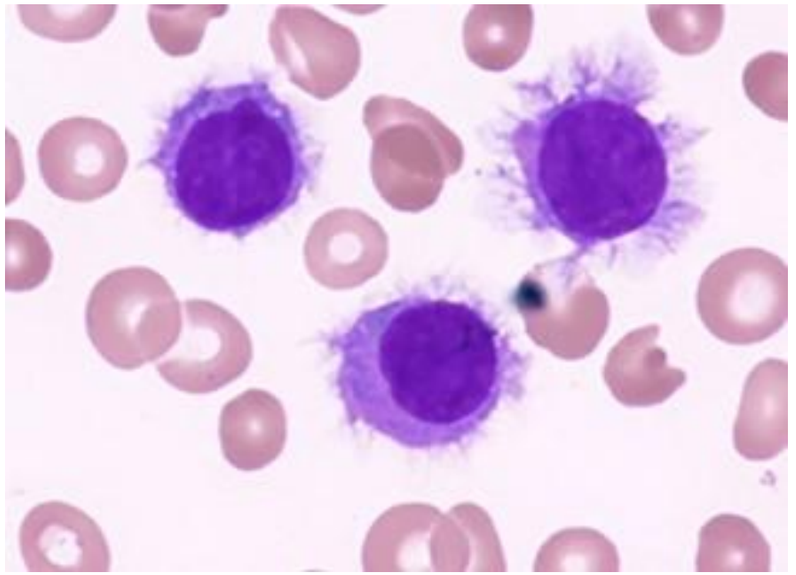
- Very high ESR (erythrocyte sedimentation rate is increased too much because of the in vivo rouleaux formation, which is a characteristic for multiple myeloma)
- CRAB (hypercalcemia (remember that this hypercalcemia results in cardiac, neural and renal symptoms), renal failure, normocytic normochromic anemia, bone fracture (X-ray shows multiple bone lytic lesions, hence the name))
- Amyloidosis: occurs in few patients, secondary to deposition of light chain (either κ or λ) in large amounts (AL-amyloid). In multiple myeloma, the abnormal plasma cells produce much more light chains that heavy chains, these excess light chains wouldn't find any heavy chains to bind, hence, these light chains start to accumulate in tissues forming damaging precipitates. For example, these proteins can accumulate in the heart causing restrictive cardiomyopathy, or in the endocrine organs causing endocrinopathies, this is known as AL-amyloidosis and it is unique for MM, however, amyloidosis in not common in MM.
- There is another type of amyloidosis known as AA-amyloidosis, this type occurs due to deposition of a protein known as serum amyloid A which is an acute phase reactant, this type of amyloidosis occurs in some inflammatory diseases, but not in MM.
- In advanced disease: pancytopenia due to infiltration of BM, plasma cell leukemia, visceral damage
- Slowly growing, hence not curable with conventional chemotherapy, so treatment of MM is difficult
- Lenalidomide: a drug of the thalidomide family, unknown MAO, but it inhibits oncogenic proteins
- Proteasome inhibitors: inhibit degradation of misfolded proteins When it accumulates, it causes apoptosis in plasma cells, this is a characteristic of plasma cells, (proteasomes are normal cellular enzymes whose function is to degrade misfolded proteins).



Lytic lesions

HAIRY CELL LEUKEIMA

- Uncommon low-grade B-cell leukemia
- Affects older patients, more common in men, smokers
- Leukemic cells are few in number, have prominent cytoplasmic projections (Spikes), hence the name, both of these properties are characteristic.
- Splenomegaly, pancytopenia (Leukemic cells heavily infiltrate BM and spleen)
- Leukemic cells are biologically active, inhibit hematopoiesis and cause bone marrow fibrosis . Pancytopenia might occur even before invasion of the bone marrow by leukemic cells, causing a clinical picture like aplastic anaemia, in that case, the bone marrow appears empty upon examination.
- LN involvement is very rare
- Mutation in serine/threonine kinase BRAF gene , this mutation is commonly found in solid tumors, like melanoma, but hairy cell leukemia is unique among lymphoid malignancies in having this mutation.
- There are certain drugs that have been approved for treatment of melanoma and hairy cell leukemia, these drugs are basically antibodies that bind to the mutated BRAF protein.
- Very indolent and very sensitive to chemotherapy

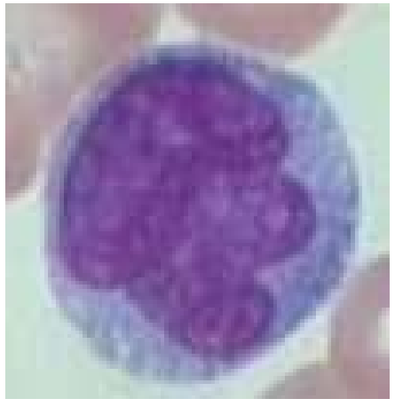


PERIPHERAL T CELL LYMPHOMA

- Most common mature T-cell lymphoma
- Can affect lymph nodes or can be extranodal, no specific pattern.
- Aggressive, poor prognosis (generally, T cell lymphoma tend to be more aggressive than B cell lymphoma)
- Neoplastic cells mimic normal T-cells, they secrete inflammatory cytokines, causing severe inflammation, so the patients are very ill, even if the tumor is very small.
- Positive for CD2, CD3, CD5, CD7 (T-cell markers) but negative for TDT which is a lymphoblastic marker.

CUTANEOUS LYMPHOMAS: MYCOSIS FUNGOIDES AND SEZARY SYNDROME

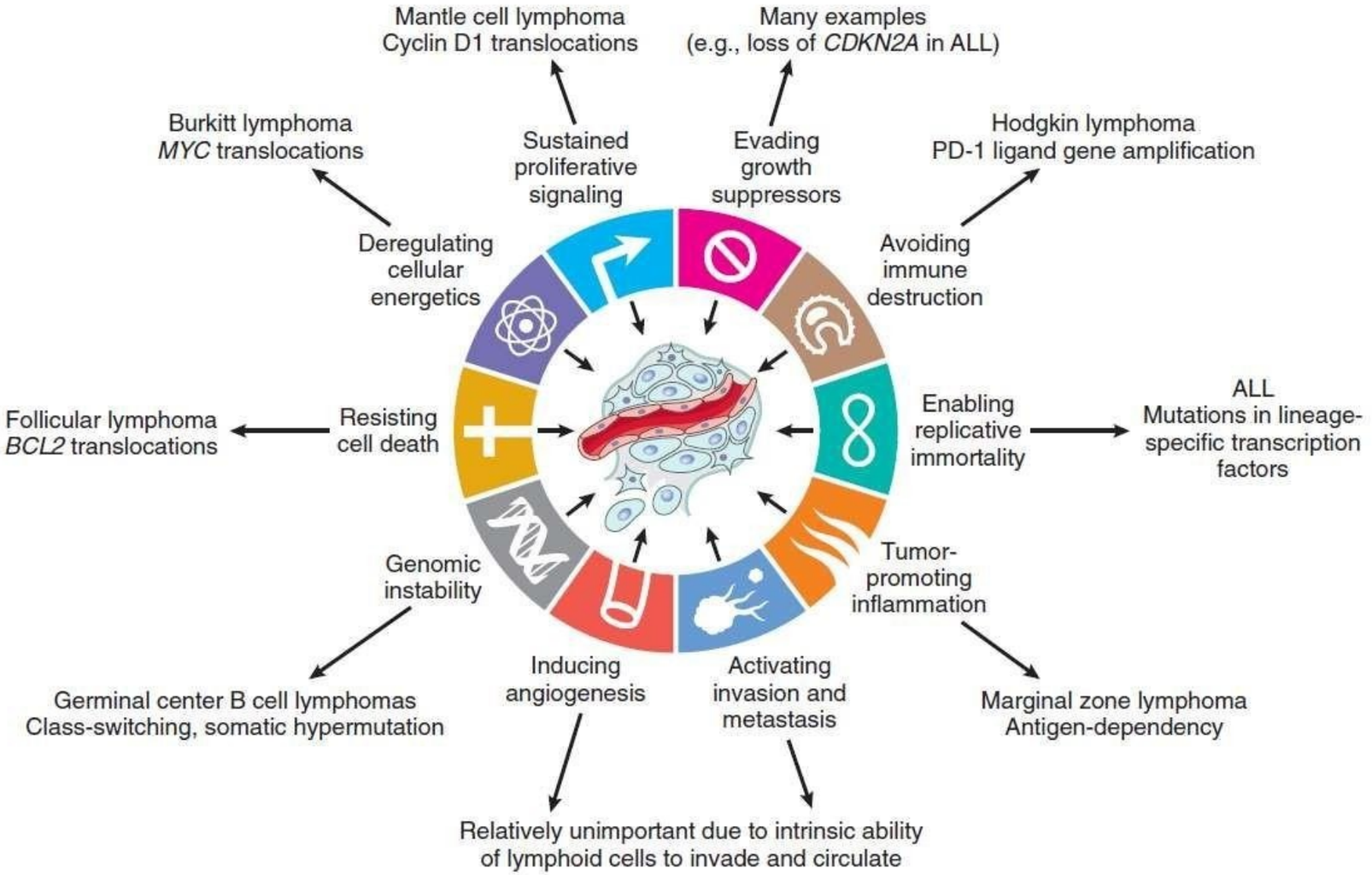
- Mycosis fungoides is a cutaneous lymphoma that arise from Neoplastic CD4+ T-cells (T helper cells) that home to skin, the name means "mushroom" 🍄 referring to the gross appearance of the tumor.
- It is the most common cutaneous lymphoma.
- Patients present with erythema, progressive to plaque, then tumor (patients usually have a long history of erythema, then the erythema suddenly progresses into a plaque and then a tumor).
- Neoplastic lymphocytes have irregular nuclear membrane (cerebriform), the cells infiltrate the epidermis and dermis, but they mostly start in the junction between them.
- With disease progression, lymphoma disseminates to LNs and viscera and it becomes fatal.
- Sezary syndrome: a rare leukemic variant of MF, patients present initially with widespread erythema affecting the whole body and blood leukemia of neoplastic cells (Sezary cells).



the nuclei of Sezary cells are irregular, similar to the gyri of the brain, so we call their appearance cerebriform. cerebrum means brain, we see them in the skin in MF and in peripheral blood in Sezary syndrome

ADULT T-CELL LEUKEMIA/LYMPHOMA

- Neoplastic CD4+ T-lymphocyte
- Caused by a retrovirus (same family as HIV); human T-cell leukemia virus 1 (HTLV-1)
- Endemic in Japan, Caribbean basin, West Africa and some parts of South America but rare in the middle east.
- Sporadic everywhere, both sporadic and endemic cases are caused by the same virus.
- Virus is transmitted through body fluids (blood, breastfeeding, sexual intercourse)
- 5% of carriers of this virus develop a neoplasm, after a latent period of 40-60 years
- It is unknown how this virus causes the tumor, but the most incriminated protein is called Tax protein, Tax protein is essential for viral mRNA transcription, it 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 a disseminated disease, involving skin lesions, lymphadenopathy, lymphocytosis, hepatosplenomegaly and hypercalcemia
- Neoplastic cells express CD25 (IL-2 receptor) this is characteristic of this cancer.
- 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