We've one category for lymphoid neoplasm which is the lymphoma in contrast to that of myeloid which has three categories; acute myeloid leukemias, myeloproliferative & myelodysplastic disorders.

Lymphoma

-Is a neoplastic disease of lymphocytes (B or T cells).Both of them cause lymphoma.
-Most commonly arises in LNs (most common) where the lymphocytes normally reside but also can present in the extra-nodal sites (Extra-nodal lymphoma) and they're less common.
-Lymphocytes exist in every organ in our body; GI, respiratory tract…
-If a neoplastic lymphosites go to the peripheral blood or reach the BM and proliferate there then it's a lymphoid leukemia (lymphoma affecting the BM & blood).

-Lymphoma is very heterogenous (having many types), much more even than myeloid neoplasms.
-They vary widely in their clinical presentation, behavior and grade (high & low).
*__Low grade__: - slow proliferation, mature cells and long course of the disease.
*__High grade__: - fast proliferation, disease progression is fast so they need intensive chemotherapy.
-That's a general classification according to their morphology and behavior and there's another classification according to the type of lymphoma; Hodgkin & non-Hodgkin lymphomas, latter one is more common.

-In most cases of lymphoma there're NO specific risk factors but, in general**, immune suppression** (for ex. pts with HIV), **chronic persistent inflammation** (for ex. H-Pylori associated gastritis; so these lymphocytes which are proliferating for a prolonged time they gain mutation and can develop lymphoma), **viruses** (1.EBV, which is a known cause of lymphoma, in most types of lymphoma, the malignant lymphocytes have EBV, so it can transform the lymphocytes. 2. HPV8 *less common*).

-The maturation and levels of lymphocytes are more complex than that of myeloid.
*As we know, B-cells start in the BM (so they're called B-cells) and get mature there. While T-cells migrate early in life to the thymus and reside there, so T lymphoblastic lymphoma only starts in the thymus.
-T-cells' maturation is a few steps, while B-cells' maturation has a prolonged course (we aren't requested to know the details)
<u>*Just know the lymphomas that can arise in the BM, which are:</u>
-lymphoblastic lymphoma/leukemia.
-Chronic lymphocytic leukemia (mature one).
-Multiple myeloma (plasma cell tumor).
*While the rest of lymphomas, arise in the LNs.

*How pts present with lymphoma?
-As we said, most commonly, it arises in LNs, so the LNs become enlarged (more than 2 cm). It's painless, taking a long time (if it's painful, then it's an acute process and lymphoma is a chronic disease).
*There're symptoms which are common for lymphoma (**B-symptoms**). They're a systemic ones, the body is affected by the tumor itself. Pts will have fever, weight loss, anorexia, night sweating…
-If B-symptoms are present, that indicates that the disease is strong.

-A neoplastic lymphocytes cause a rxn in the body so some pts present with B-symptoms indicating a worse disease.
-Immune suppression is a risk factor, but also if a pt without immune suppression and develops lymphoma, he'll suffer from a secondary immune suppression.
(So there's a relation between lymphoma and immune suppression; large # of neoplastic lymphocytes suppresses the function of the normal immune system.)
Pts with lymphoma are commonly suppressed and more liable for infections.

-High LDH, like the hemolytic anemia, lymphocytes have LDH and when they become neoplastic, large # will be destructed releasing their LDH.

-When the pathologist examines LNs under the microscope, he'll see abnormal architecture (the architecture consists of the follicles "B-cells" and in between them "T-cells") and lymphoma originates either from T or B cells→ proliferation → effacing the whole architecture. (Always we've abnormality in the architecture)
B lymphomas are much more common than T ones.

-If we've a lymphoma and we want to know its type (B or T), normally B-lymphomas express Ags on their surface CD19 & CD20→ B-lymphocytes' markers, while T-cells express CD2 & CD3. *v.imp. to know this point*

*We'll only talk about the most common types of lymphoma.

1) Acute <u>lymphoblastic</u> leukemia / lymphoma (ALL)

-This type يُقابل the acute myeloid leukemia. It's a rapid disease, sudden onset, progressive, high grade, NO maturation so they're lymphoblasts which are the 1st cell in the lymphoid-line (that's all the meaning of ACUTE).
-It's called "**leukemia**" because it commonly arises in the BM and circulates in the blood, but if they arise in the LNs, much less common, we call it "**lymphoma**".
-In acute myeloid leukemia, there's NO tissue counterpart (rarely go outside and invade tissues), but ALL prefers to go and reside in tissues and proliferate there also, producing a tumor related to that tissue and this is another cause that why we call it "lymphoma". So it arises from the BM, and circulates in the blood.

-Pts with T-ALL have a mediastinal mass "thymus is growing".
-Lymphoblasts, like AML, develop mutations that transform this normal lymphoblast.
-So, they've a problem in the maturation, they don't differentiate and a problem in the mitosis, having a high mitosis. Lymphblasts proliferate in a high # and destroy the normal BM elements.

-Like AML, we call it lymphoblastic leukemia when the <u>lymphblast count exceeds</u> **<u>20% or more</u>**.
-Myelophthisic *destruction of the normal BM*.

-Clinically, like AML, pts will have sudden progressive symptoms. It's related to the decrease in neutrophils.
-All the erythroid cells are destroyed, so pts will suffer from a severe anemia.

-Even the brain, it can be invaded and less commonly testes in males.
**AML stays in the BM and blood.

-There's a slide showing two pictures which illustrate the differences between AML (B) & ALL (A).
*Both of them are blast (myeloblast & lymphoblast) and acute leukemia.
-Myeloblast has a clear cytoplasm in contrast to that of lymphoblast.
"Lymphoblast is smaller in size with less cytoplasm"
-Myeloblast has a prominent multiple nucleoli while in lymphoblast they're less in #, and sometimes we don't see them!

2) *Chronic <u>lymphocytic</u> leukemia* CLL** (in the BM & blood)

-The cells are most mature. It تُقابل the CML.
-If they go to the tissues, we call it **"small lymphocytic lymphoma *SLL*"**
-Low grade B-cell lymphoma (there's NO T-cell).
-It's the disease of elderly (children are NOT involved) in contrast to the previous one.
-Looking similar to normal lymphocytes but with high #.

-**Bcl2** (B-cell lymphoma), which is an anti-apoptotic protein (normal function).
*This gene will be up-regulated, so lymphocytes will survive for longer time. Ending up with a higher # and the pic. Of lymphoma/ leukemia.
-It causes a hemolytic anemia (Autoimmune/Cold Agglutinin Type).

-10% gets more mutations and transforms into high-grade lymphoma.
{In general, it's a good disease}.
-When progression starts, we begin in the Tx.

Morphology

-Abnormal architecture in the LNs, germinal centers are absent.
*There's a slide showing a pic at high power, in between B-cells, there're scattered larger immature cells (**prolymphocytes**), coming before the normal lymph *arrow*.
-So in progression we said 10% (prolymph) becomes predominant (more aggressive).

-In the peripheral blood (blood film) → large # of cells.
*__Smudge__: easily broken cells.

3) Follicular lymphoma

-Common in the western countries, it's common in our region but NOT the commonest one.
-Arises from the follicles and that's why it's called Follicular lymphoma.
-Lymphoma cells have a specific translocation, which is diagnostic and present in all cases.
-IgH gene is very active.
-Generalized lymphadenopathy → in the LNs of the whole body.

*Under the microscope we'll see large LNs full of follicles.
-Like CLL, pts have indolent course but the chance of transformation is higher (40%).

-There should be a distance between the follicles for T-cells (in normal cases), but here they're crowded.
-**Small cleaved cell lymphoma** can be noticed at high magnification (elongated cells).
-With progression, centroblasts will be predominating.

4) Diffuse large B cell lymphoma

-Diffuse: No architecture, effacing the LNs.
-Large: the size is more than the double.
-Aggressive type of lymphoma.
-Also arises in children (less common).
-Arises de novo (from the beginning) and this is in most cases or it can complicate other low-grade lymphoma (CLL & follicular lymphoma which when they transform, they'll transform to this one).

Risk Factors:

-Chronic Immune stimulation (NOT specific for this type).
*If not treated with chemotherapy, it'll kill the pt quickly.

5) Burkitt lymphoma

-Have specific properties that distinguish it from other types of lymphoma.
-The fastest growing known cancer in the human, the $t_{1/2}$ of cells is 8 hrs.
- Affect children, in contrast to diffuse large B cell lymphoma.
-Extranodal sites (solid organs).
-EBV is common in respiratory tract and oral cavity.
-Symptoms assemble the appendicitis, but actually it's a tumor.

Pathogenesis: t (8:14), myc gene encodes transcription factors for the cell cycle.

*High-grade → responds to chemotherapy.
*Low-grade → long duration of mitosis, doesn't respond to chemotherapy.
So that we leave pts for a period of time until cells become more active then we start treating them.
chemotherapy works at the time of mitosis

-The tumor cells aren't large (intermediate size) and they're all the same (one type) → under the microscope.
-At the low power, we'll see white areas → **Starry sky.**
-These areas are died cells due to the high proliferation, so macrophages will phagocyte the apoptotic cells.

Hodgkin lymphoma

-Old known lymphoma, pts come with enlargement LNs esp. in the upper part of the body.
-Its progression is distinctive, starting in the neck, mediastainum, axillary, abdomen, spleen, liver, BM then into solid organs.
-Other lymphomas → generalized lymphadenopath, BM or extranodal.
-When it was discovered by the British surgeon Hodgkin, it's thought that is s.th inflammatory! And he described it clinically.

-These cells are giant, have two nuclei with two prominent nucleoli → **Reed-Sternberg cells***RS cells* (they're called so because of the 2 pathologists who examine these cells under the microscope but they didn't know that they're malignant lymphocytes).

-The neoplastic cells are very few and that makes a difference from other types of cancer in human. The mass of the tumor is formed by the normal cells.
CD20 is absent. CD20 & CD3 are –ve but +ve for CD30.

Plasma cell tumors → Plasma cells myeloma

-Arise from the long-lived plasma cells (memory cells) in the BM.
-Pts have monoclonal gammaproteins (M-proteins), high quantity of them in the blood causing significant symptoms alone without the plasma cells.
-It's 10% of all BM tumors (without lymphoma & leukemia).
-Difficult to eradicate , doesn't respond to chemotherapy because they don't divide, they live for a long time but after a period of time they suddenly divide to produce another clone so we cannot give chemotherapy continuously ,just at the time of mitosis.
-Don't affect children.

Risk Factors:

-Old age, more common in males, more common in Africans, radiation, family history and recently described that the obesity is a risk factor!

-Accumulation of genetic mutation and also chromosomal aberration (so these cells are full of mutations).
-Plasma cells have a strong interaction with the normal stromal cells (surrounded environment); endothelial cells of capillaries, fibroblasts, osteoblasts…
*So one of the Tx is to target the stromal cells (e.i. destroying the capillaries, so these cells will be more reliable to death).

-Neoplastic plasma cells secrete Igs; and most commonly IgG.
-In the BM, plasma cells count > 10% ((normally is up to 3%)).

Clinically:

-Pts will always have bone pain ((like the acute lymphoblastic leukemia)).

*That's because these plasma cells can activate osteoblastic cells → erosion of the bone → osteopenia.
-Bone trabeculae will be thin, more reliable for fracture and Ca^{++} will exit causing hypercalcemia.
-They've commonly renal failure because M-proteins are produced in a large amount and stuck together so causing obstruction to the renal tubules.
-They've amyloidosis which is very bad; it can accumulate in the tissues and destroy them (heart, kidneys, BM). Amyloid is formed from part of Igs *light chain*.
-They've anemia; normocytic normochromic because of the decrease in the production.
*Plasma cells suppress the normal erythropoesis by mediators, also when they're increased in # they'll destroy the normal erythrocytes (effacement) → leading to decreased production.
-Recurrent infection; this abnormal Ig interferes with the function of the other normal Igs.
-Also there'll be a hyperviscosity; M-proteins affect the movement of RBCs.

Morphology:

*Malignant plasma cells are larger, having multi-nucleation, prominent nucleoli.

-Special setting disease * **monoclonal gammopathy of undetermined significance** *→ between 3-10 %
They're asymptomatic, and this is a previous stage coming before myeloma.

-In peripheral blood→ plasma cell but normally it doesn't present (Zero).

-There's a slide showing X-ray pic. → There're spaces (osteolytic regions) due to myeloma.
-Special feature: Igs cause RBCs to stick together in a special morphology (linear) in contrast to that of agglutination which is in all directions (hemolytic anemia)
This feature → **Rouleuax formation**

NOTE: as you know, the new slides are NOT available -.-", so we depend on the previous ones, and there're differences between them! So this is MORE than extra-notes!

Great luck ☺

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