HEMATOLOGY
&LYMPH SYSTEM

Pathology sheet

Number	7
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Neoplastic Disorders of White Blood Cells

-**Leukemia**: neoplastic leukocytes circulating in the peripheral bloodstream.

-**Lymphoma**: a neoplastic process in the lymph nodes, spleen or other lymphatic tissue.

These sites are the most common but they're not exclusive, i.e. we may have lymphoma with neoplastic cells circulating in the blood, or we may have leukemia presenting as masses.

-**Acute**: The neoplastic process involves early immature precursor cells.

-**Chronic**: The neoplastic proliferation is presented by some degrees of differentiation (mature precursor cells).

Note: The terms “acute” and “chronic” don't necessarily refer to the period of time it took the neoplasm to appear; it's all about cell differentiation.

We have three major types of WBCs neoplastic disorders:

I. **Lymphoid neoplasms**
II. **Myeloid neoplasms**
III. **Histocytic neoplasms**

I. Lymphoid Neoplasms

Lymphoid neoplasms are subdivided into:

A. **T-cell neoplasms**
B. **B-cell neoplasms**

Tumor cells could present as:

1. Leukemia like chronic lymphocytic leukemia (CML).
2. Lymphoma like Hodgkin Lymphoma (HL).
3. Plasma Cell neoplasm like Plasma Cell Myeloma (Multiple Myeloma).

They all have overlapping clinical features (generalized lymphadenopathy, weakness, fatigue, weight loss... etc), and none of them are specific; therefore, clinical presentation here doesn't have much of an importance in diagnosis. Classification depends on the cell of origin (found using the microscope).

-Normal lymph node cells are derived from different stem cells which means they show different types of antigens; therefore, they're **Polyclonal** = not malignant.
-All lymphoid neoplasms are derived from a single transformed cell, so they're **monoclonal** = malignant.

Assessment of clonality can be done by:

a- Immunophenotying (expressing only kappa or only lambda gene), or by
b- Genetics (receptor gene rearrangement).

There's a relationship between lymphoid neoplasms and immune system for some reasons, so lymphoma patients may develop immune abnormalities, also autoimmune disorders will increase the risk of malignancies.

-Lymphoma has the potential to spread anywhere in the body.

**Remember: B & T lymphocytes arise from the lymphoid stem cells in the bone marrow, then B-cells mature in the bone marrow, while T-cells maturation takes place in the thymus.

-Lymphoid neoplasms are:
1. Precursor B and T cell lymphoblastic lymphoma/leukemia, commonly called **Acute Lymphoblastic Leukemia (ALL)**.
2. **Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma**.
3. **Follicular Lymphoma**.
4. **Mantle Cell Lymphoma**.
5. **Diffuse Large B Cell Lymphomas**.
6. **Burkitt Lymphoma**.
7. **Multiple Myeloma** and related plasma cell tumors.
8. **Hodgkin Lymphoma**.

1. Precursor B and T cell lymphoblastic lymphoma/leukemia, commonly called acute lymphoblastic leukemia (ALL)

- **B** cell lymphoblastic leukemia
  - Majority of the cases (85%).
  - The most common malignancy in children.
  - Peak age: 3 years.
- **T** cell lymphoblastic leukemia
  - Minority of the cases (15%).
  - Called **Thymic Lymphoma** because it presents as a mass in thymus.
  - Peak age: adolescence.

Morphology:

B-ALL: Hypercellular marrow
T-ALL: Cellular thymus or lymph nodes

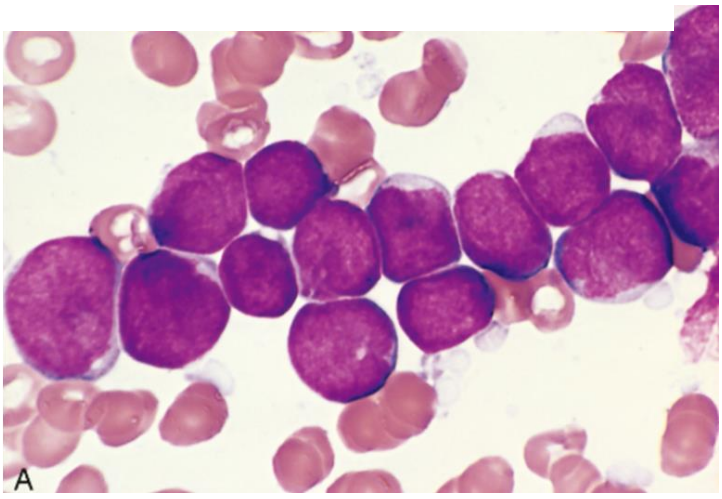

Figure1: Blasts, fine chromatin & prominent nucleoli.

There're large malignant stem cells with small cytoplasm, large nucleus, fine chromatin and prominent nucleoli called **Blasts.**

****Note:** Blasts are the only cells in the hematolymphiod system that have fine chromatin and prominent nucleoli.

In routine staining, there's no difference between B and T leukemia, immunophenotyping is needed to identify the markers on the cell either by immunostains or by flow cytometry.

- **CD19**, CD79, pax5, CD22 and CD20 indicate B cell origin, CD19 is the most specific.
- **CD3** is the most specific T cell marker.
- TdT indicates early immature B or T lymphocytes, but not myeloid.
- CD34 indicates early immature B or T or myeloid cells.

For example: if we have a tumor with these markers: CD34+ , TdT+, CD19+, we will diagnose it as B-cell acute lymphoblastic leukemia.

Genetics:

In B-ALL, a translocation mutation may occur between:
- (12; 21) genes, which carries good prognosis.
- (9; 22) genes, which carries bad prognosis.

In T-ALL: (NOTCH, PTEN, CDKN2A) genes are mutated.

Clinical features:

- Depression of bone marrow.
- Mass effect, mostly in T-ALL because it presents as a mass in the thymus.
- CNS manifestations, B-ALL cells in children are known to attack the CNS cells and meninges causing vomiting, headache... etc.

Acute lymphoblastic leukemia is an aggressive, highly-curable tumor, with 80% cure rate in children, and 40% in adults.

The following are the good/bad prognostic factors of ALL:

Bad prognostic factors	***Good prognostic factors***
Age < 2, or > 10	Age between (2 and 10)
WBCs count > 100,000	Low WBCs count
Normal ploidy or hypodiploidy	Hyperdiploidy
Translocation mutation between (9; 22) genes	Translocation mutation between (12; 21) genes

2. Chronic lymphocytic leukemia (CLL) & small lymphocytic lymphoma (SLL)

- Chronic lymphocytic leukemia (CLL): When PB count of neoplastic cells is > 5000/microliter.
CLL is the most common leukemia in general.

- Small lymphocytic leukemia (SLL): When PB count of neoplastic cells is < 5000/microliter, with lymph node involvement.

Morphology:

-Small mature lymphocytes that appear like normal lymphocytes with dense chromatin and small nucleoli. A small percentage of lymphocytes show prominent nucleoli, called **Prolymphocytes**.

If lymph nodes are involved, they will be effaced with sheets of lymphocytes.

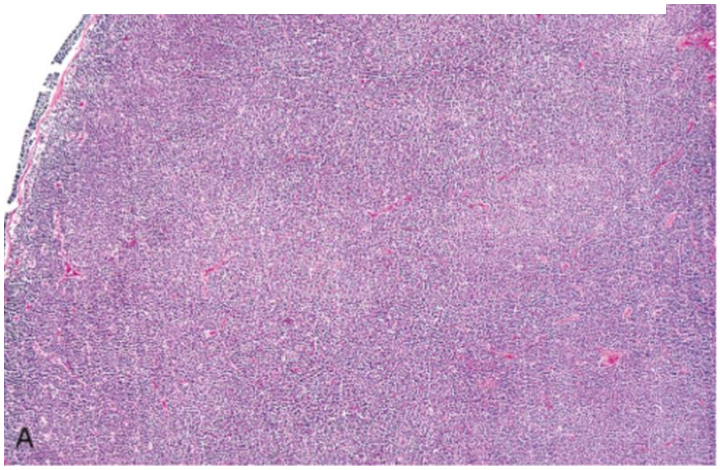

Figure 1: Lymph node effaced with sheets of lymphocytes

Immunophenotype:

- CLL is a B-cell neoplasm, so B-cell markers (CD19, CD20, CD22, CD79, pax5) will be positive.

- CD5 is positive (although it's a T cell marker).
The other CD5 positive B cell lymphoma is mantle cell lymphoma.

Clinical manifestations:

- They are usually old in age.
- Asymptomatic.
- Nonspecific symptoms like fatigue, anorexia, lymphadenopathy... etc.
- Lymphocytosis.
- Hypogammaglobulinemia, and 15% of them have autoimmune warm hemolytic anemia.
- Good prognosis, they live for 10-15 years (prolonged survival).
- Not curable without stem cell transplantation, and only in young patients.
- Small fraction might progress into diffuse large B cell lymphoma (DLBCL), with a survival period of less than one year.

3. Follicular lymphoma

Follicular lymphoma is caused by a translocation mutation between (14; 18) genes, placing BCL2 (antiapoptotic) gene under the control of IgH active gene, inhibiting the apoptotic pathway & causing malignancy.

Morphology:

Lymph nodes are effaced by follicular (nodular) arrangement of centrocytes (small cells with cleaved nucleus), and centroblasts (large cells with nucleus containing basophilic membrane-bound nucleoli).

Immunophenotype:

- Follicular lymphoma is a B-cell neoplasm, so B-cell markers (CD19, CD20, CD22, CD79, pax5) will be positive.

- CD10 is positive
The other CD10 positive tumors are B-ALL , Burkitt lymphoma, and some cases of DLBCL.

Clinical manifestations:

- Patients are usually older than 50 years.
- Generalized lymphadenopathy.
- Bone marrow is involved in 80% of cases.
- Not aggressive, patients can live 10 years (prolonged survival).
- Not curable.
- 40% of cases (worse than CLL) transform into DLBCL, with dismal (very bad) prognosis.

4. Mantle cell lymphoma

Mantle cell lymphoma is caused by a translocation mutation between (11; 14) genes, placing Cyclin D1 gene under the control of IgH active gene, increasing uncontrolled cell proliferation and causing malignancy.

Morphology:

- Lymph nodes are effaced by sheets of medium sized cells with similar morphology to mature lymphocytes, while a small percentage of cases have blastic morphology. From here you can notice that morphology isn't that important in diagnosis; it's all about the Immunophenotyping.
- Bone marrow is involved in most cases.
- Sometimes mantle cell lymphoma results in GI polyps.

Immunophenotype:
- B-cell markers are positive.
- CD5 is positive (similar to CLL).
- Cyclin D1 is positive (CLL is negative for Cyclin D1).

Clinical manifestations:
- General nonspecific symptoms.
- Lymphadenopathy.
- Not curable, patients live for 4-6 years with treatment only.

5. Extranodal marginal zone lymphoma

This tumor is a low grade B cell neoplasm arising in tissues such as GI, thyroid, skin, salivary gland and orbit. In these tissues it's associated with chronic inflammation whether infectious or autoimmune.

Morphology:

- Lymphoepithelial lesions, tumor occurs usually out of the lymph nodes, in organs with epithelial lining like in GI, where lymphocytes will attack the epithelium.
- lymphocytes are small to medium in size with variable cytoplasm.

Immunophenotype:

- B-cell markers are positive.
- There's no specific marker to diagnose extranodal marginal zone lymphoma.

Clinical manifestations:

- A mass at the site of involvement, like enlarged thyroid, or ulcers in the stomach.
- It's a low grade disease, with prolonged survival, without any cure, except gastric MZL secondary to H.pylori infection. Once eradicating H.pylori, the patient will get cured.

6. Diffuse large B cell lymphoma

Diffuse large cell lymphoma is the most common lymphoma in adults. It's either de novo (primary) or a transformation from other low grade tumors (secondary), especially CLL and Follicular lymphoma.

Morphology:

Hence the name, it presents as large cells with at least double the size of a normal lymphocyte, with diffused arrangement; appears like ALL blasts under the microscope.

Immunophenotype:

- B-cell markers are positive.
- CD10 in a subset of cases is positive (mentioned before).

Clinical manifestations:

- Patients are usually older than 60 years of age, but DLBCL can occur at any age.
- Generalized lymphadenopathy.
- DLBCL can occur in extranodal sites like in skin or GI, similar to EMZL.
- DLBCL is very aggressive and rapidly fatal if not treated.
- With treatment it can be cured in 50% of cases.

Notice: High grade tumors are usually aggressive (immediately cause death if not treated) and highly curable, while low grade tumors are usually associated with prolonged survival and small chances to be cured.

Remember:

CLL: The most common leukemia.
ALL: The most common leukemia in children.
DLBCL: The most common lymphoma.

-CD5 positive tumors:
CLL and mantle cell lymphoma.

-CD10 positive tumors:
Follicular lymphoma, B-ALL, Burkitt lymphoma and some cases of DLBCL.

Record 7 ends here.

7. Burkitt lymphoma

A B-cell lymphoma, the fastest growing tumor in humans, and presents as 2 types:

1. **Sporadic**: in all over the world, presented by abdominal masses.

2. **Endemic**: in Africa, where it's highly associated with Epstein-Barr virus (EBV) infection, presented by mandibular or maxillary masses.

Both are usually extranodal diseases, and are common in young children.

Burkitt lymphoma is caused by a translocation mutation involving MYC gene on chromosome 8, the most common translocation is between (8; 14) genes.

Morphology:

- Sheets of medium sized lymphocytes with variable cytoplasm and several nucleoli forming a Starry-sky appearance.
- A lot of mitotic figures (Frequent mitosis).

Ki67 is a stain used in pathology to determine the percentage of proliferating cells, for example Ki67 for DLBCL (aggressive tumor) is 40-50%, Ki67 for the most aggressive lung tumor is 10-20%.

Burkitt lymphoma is the only human neoplasm with Ki67 more than 99% (nearly 100%), which means that Burkitt lymphoma is very aggressive.

Immunophenotype:

- B-cell markers are positive.
- CD10 is positive (as mentioned earlier).
- BCL2 is negative. (Remember that BCL2 is positive in follicular lymphoma).

You have to know all markers for each tumor

Clinical manifestations:

- Patients are usually young adults or children.
- Peripheral blood is involved in the majority of cases of burkitt lymphoma, and here we should distinguish between burkitt lymphoma and B-ALL by CD34 or TdT markers (ALL is CD34, TdT positive and burkitt lymphoma is CD34, TdT negative).
- As mentioned before, Burkitt lymphoma is very aggressive tumor, and like any other high grade tumor burkitt lymphoma is a curable tumor.

Questions:

1- The most specific markers for T cell differentiation is:

A. CD19
B. CD10
C. CD20
D. CD3
E. CD79

Answer: D

2- All the following are good prognostic factors in B-ALL, except:
A. Age 2-10 years
B. Low WBCs count
C. Translocation between (21:21) genes
D. Hypodiploidy
E. Translocation between (9:22) genes

Answer: D, E

3- The most common lymphoma is:
A. Follicular lymphoma
B. Burkitt lymphoma
C. DLBCL
D. CLL
E. Mantle cell lymphoma

Answer: C

4- What tumor is positive for Cyclin D1?
A. Follicular lymphoma
B. Burkitt lymphoma
C. DLBCL
D. CLL
E. Mantle cell lymphoma

Answer: E

5- *MYC* gene translocations are associated with:
A. Follicular lymphoma
B. Burkitt lymphoma
C. DLBCL
D. CLL
E. Mantle cell lymphoma

Answer: B

The End