Hematology

- Histology
- Biochemistry
- Pathology
- Pharmacology
- Physiology
- Microbiology

- Handout
- Slide
- Sheet 7

- Dr. name :
  Dr Tareq Aladily
- lecture number :
  7
- Done BY :
  Salsabeela Bani Hamad

By: Amer ABU Shmais

Lymphoid Neoplasms

Note: the dr explained lymphoid neoplasm before acute lymphoid leukemias so don't get confused when referring back to the slides.

Lymphoid neoplasms:

Also called **lymphoma**, it is the malignant neoplasm of lymphocyte. Neoplastic disorders originate from **B or T lymphocytes** and most commonly arise in **lymph nodes** as it is the original site of lymphocytes. The lymph node differ from solid tissue, the lymphocyte can circulate in the blood so in any lymphoma there is a possibility that malignant cells go out and circulate in the blood. If it circulates in peripheral blood, it is called lymphoid leukemia. Lymphoma is very heterogeneous; meaning there are so many types, it is probably the most numerous type of cancer.

There are so many types and they vary widely in their clinical presentation and behavior. Generally, **we classify them into**:

- **Low grade lymphomas;** that proliferate very **slowly** and the disease stays for a long period of time, for years, if it is not treated it stays for a long time until it progresses and transforms into a high grade.
- **High grade lymphomas;** the clinical course is **sharp**, the symptoms progress **rapidly**, the size of the tumor will increase in a short period of time, and if not treated it will cause **death** quickly.

Another classification for **B lymphomas** specifically**:**

- **Hodgkin lymphomas**; most common type of lymphomas in children, while they constitute only 1/3 of all B lymphomas in adults.
- **Non-Hodgkin lymphomas;** most common lymphomas in adults.

Risk factors of lymphomas:

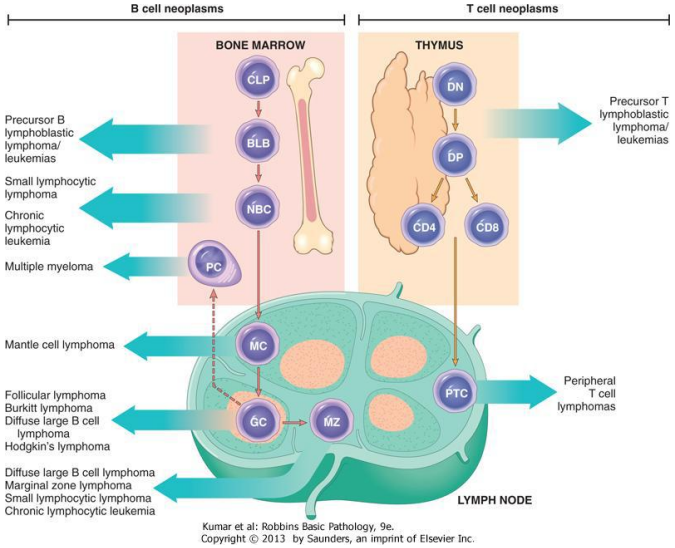
- As any type of cancer, most cases don't have clear cause, but in some cases there is an obvious cause that precedes the development of lymphomas, for ex:
  1. Immune suppression; it is associated with all types of cancer; actually it is a risk factor for cancer.
  2. Chronic inflammation; any chronic persistent of inflammation in the body like in autoimmune diseases, the persistent proliferation of cells increase the tendency of gaining mutations.

Written by سلسبيلا فاروق بني حمد

In chronic inflammation the lymphocytes are continuously active i.e. they proliferate in a continuous manner, so they build up mutations and transform into cancer cells.

3. Viruses; they are very common in lymphomas, each type of virus can cause many types of lymphomas, ex:
   - EBV (Epstein-Barr Virus); it causes many types of lymphoma. EPV is positive in malignant cells of many types of lymphomas.
   - HHV8 (Human Herpesvirus-8); also can cause certain types of lymphoma but it is less common.

This is a general scheme of normal lymphogenesis in the body which shows the site of development of lymphocytes.



- **B lymphocytes** are produced and become immunocompetent in the **b**one marrow, then they circulate and go to the lymph nodes and in germinal centers they proliferate to produce B memory cells and plasma cells, **most** of these plasma cells go back to the bone marrow and **some** of them stay in the lymph nodes.
- **T lymphocytes** are produced in the bone marrow and become immunocompetent in the **t**hymus, then they will circulate to the secondary lymphatic tissues where they become either cytotoxic T cells, that express CD8 on their surfaces, or helper T cells, that express CD4 on their surfaces.

You have to know that in the early stages of development of T cells, when they are still immature, each cell has **double positive**, i.e. each cell will have both CD4 and CD8 then it becomes either CD4 (in helper T cells) or CD8 (in cytotoxic T cell), then they exit the thymus and go to the lymph nodes.

The abundant lymphocytes in the lymph nodes are **T lymphocytes** not B lymphocytes.

In Each step of the lymphogenesis, cells can be arrested and transformed, that is why there are so many types of lymphoma. This means when we discuss lymphomas, the first thing to mention is the stage of the **cell of origin** and from where it is transformed; is it from **germinal centers**, the mantle cell, **bone marrow**, or plasma cells (in B lymphomas) OR from thymus (in T lymphomas).

Written by سلسبيلا فاروق بني حمد

Remember that T lymphocytes are still immature in thymus and you should know that the **cancers which originate from immature nonfunctional cells are much worse than those originate from mature functional cells**, because they are aggressive and don't respond to drugs while those originate from mature cells can be controlled by drugs.

Diagnosis:

{(1-4) are at clinical level, (5-6) are at microscopic level}

1. Commonly, there is a mass (enlargement of the lymph node like solid tumors) and its size is **more than 2 cm**.
2. Sometimes patient will develop **B-symptoms**; which indicate that there is a **systemic influence** for the tumor, in this case patient has **fever, night sweating, weight loss, anorexia**. Presence of B-symptoms indicates a worse disease.
3. **Immune suppression** is also common either preceding the tumor or after developing of lymphoma. In lymphoma, predominant lymphocytes are the neoplastic one which can't function well, and they suppress the function of the normal immune response. So lymphoma patient is immunosuppressed; although he has high number of lymphocytes but they are not functioning well, so he is **more liable to infections**.
4. **High LDH (Lactate Dehydrogenase) enzyme level**; because it is present in lymphoma cells which are high in number and some of them will die and release LDH and this increases its level in lymphoma patient. {like Uric Acid in Polycythemia Vera that we mentioned in a previous lecture}.
5. Microscopically, the **architecture is abnormal**. We know that in the normal architecture we see germinal centers inside follicles and this is the site of B cells, while T cells present at the area between these follicles. Lymphoma originates from either B **or** T lymphocytes, so one of them will proliferate and increase in size which will cause **effacement (erase) of the whole architecture** (the normal architecture will not be present at all), in addition to increase in the size of the whole lymph node.
6. Overgrowth of B **or** T-cells; morphologically they are the same, you only see malignant cells and can't differentiate if it is B or T unless you use special stains (markers):
   - B lymphocytes express CD19 and CD20
   - T lymphocytes express CD2 and CD3. {In addition to these, Cytotoxic T cells express CD8 and Helper T cell express CD4}

For example, if you use special stain and you get CD19 positive, you conclude that this is B lymphoma.

This special stain is called **immunohistochemical stain**.

Now we will talk about the most common types of lymphoma. There are 200 types of Lymphomas but we are expected to know the following types which are the most common:

1) Acute Lymphoblastic Leukemia/ Lymphoma (ALL):

- Whenever you hear the term **-blastic** you should know it means immature (at the early stage of development), and we said that immature cells are **aggressive** and don't respond to treatment, so it is of **high-grade** type of Lymphoma or leukemia.
- We give it both terms (leukemia and lymphoma) because it can arise from both bone marrow (leukemia) and lymph nodes (lymphoma), respectively. But the cells are the same.
- It arises from precursor lymphoid cells (lymphoblasts) of either B lymphocyte or T lymphocyte. so it can be either B or T lymphoblastic leukemia/ lymphoma.
  {Remember, **lymphoblast** is the cell at the first stage of lymphogenesis and it is the most immature stage. In B lymphocyte it present in the bone marrow and in T lymphocyte in the thymus}
- **B-acute lmphoblastic leukemia/lymphoma** is **more common** than **T** and it is the most common cancer in **children**, it arises from bone marrow (BM) and circulate in the peripheral blood and sometimes it seeks outside the circulation affecting lymph nodes (LNs) and even solid organs.
- **T-acute lmphoblastic leukemia/lymphoma**, it arises from the thymus, occurs in **adolescence age** and most common in **males.** It also can circulate in the blood and affect bone marrow and solid organs.
- There are a large number of mutations in lymphomas, lymphoblasts proliferate continuously and they **can't mature**, and that is why it is leukemia (because it is immature).
- So there are many **lymphoblasts** (not **lymphocytes**).
- Lymphoblasts –as in the case of acute leukemia- exceed 20% of the total cells in the bone marrow in the case of lymphoma/ leukemia and this will cause **myelopthistic anemia**, so patients usually manifest with fever because of infections due to low lymphocytes and lymphoblasts which are not functional they will also have anemia presented with fatigue and tiredness and when you do complete blood count you will see the anemia and neutropenia, you may also find bleeding as a result of thrombocytopenia. So it destroys the bone marrow causing panctopenia.
  - Lymphocytes constitute 5% in normal people while they exceed 20% in lymphoma/ leukemia).
- When disease manifests in lymph nodes, called **lymphoblastic lymphoma**.

Written by سلسبيلا فاروق بني حمد

Clinical features:

- From the name, it is **acute**; symptoms appear progressively and in a short period of time {**Abrupt, stormy onset of symptoms**}.
- Patient will suffer from:
  - **fever** that is caused by **infections** as a result of **neutropenia**.
  - **Fatigue and tiredness** because of **anemia**.
  - **Bleeding** because of **thrombocytopenia**.
  - **Bone Pain**.
- Lymphoblasts tend to disseminate into tissues:
  - Generalized lymphadenopathy; lymph node enlargement.
  - Splenomegaly
  - hepatomegaly
  - brain involvement
  - testicular involvement

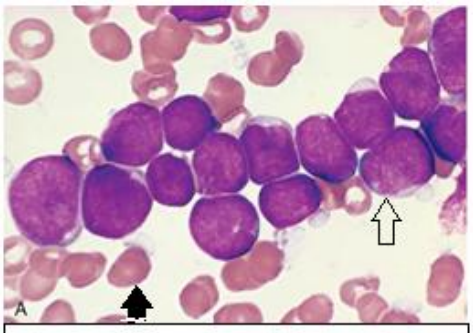
(The sites of dissemination in this disease differ from those in AML, AML has higher chance to disseminate to solid organs).

Wiki note:

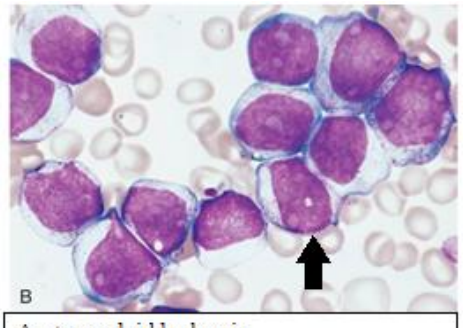
Myelophthisic anemia (or **myelophthisis**) is a severe kind of anemia found in some people with diseases that affect the bone marrow. **Myelophthisis** refers to the displacement of hemopoietic bone-marrow tissue either by fibrosis, tumors or granulomas.

Morphology:

- **Acute Lymphoblastic Leukemia/ Lymphoma**:
  - Lymphoblasts are large (larger than lymphocytes)
  - The size of **normal** lymphocyte is similar to size of RBCs. In the picture you can see the **RBCs and lymphoblasts**, and you can know that it is lymphoblast not lymphocytes because their size is larger than the size of RBCs by double or triple.
  - The lymphoblasts are large in number (more than 5%) and can be found in the bone marrow and the peripheral blood.
  - Also the color of the nucleus, it is **dark in the lymphocyte** as it is **mature**, while in the picture the color of the **immature nucleus of lymphoblast is faint (pale)** and has **no nucleoli**.
  - lymphoblasts have fine chromatin
  - The ratio of nucleus to cytoplasm is very high, the cytoplasm is present but in very minimal and it is usually empty; has no granules (**minimal agranular cytoplasm**).



Lymphoblastic leukemia/ lymphoma
White arrow represents Lymphoblast
Black arrow represents RBC



Acute myeloid leukemia
you can see the large blasts with abundant of cytoplasm, and there are nucleoli (the small white circles)

- **In Acute myeloid leukemia**, which we will talk about in the next lecture, there are blasts also but the **cytoplasm is more abundant**, and there are **nucleoli** (not present in lymphoblasts), also they have granules unlike the lymphoblasts.

Written by سلسبيلا فاروق بني حمد

2) Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma (CLL):

-It is the opposite of the acute lymphoblastic leukemia.

- Lymphocytic; means the malignant cell is **lymphocyte**, **differentiated cell**.
- Can arise from bone marrow (leukemia) or from lymph nodes (lymphocytic), so it is the same as the previous disease but with different fases.
- It is **low-grade tumor** because cells are **small**, **round**, **mature** and **looking similar to normal lymphocytes.**
- The nucleus is **dark** (like in normal lymphocytes) and have chromatin
- **Bcl-2** is anti-apoptotic protein, found normally in the mitochondria of the cell, it has a role in survival of the cell as it make balance with pro-apoptotic factors. In this lymphoma Bcl-2 is increased (up-regulated) which means the cells will have longer life and persist for a longer time, so the number of cells will increase and this manifest as leukemia or lymphoma.
- In contrast to acute lymphoblastic leukemia, this type of lymphoma is most common in elderly (doesn't appear in children). **It is the most common leukemia in elderly.**

Clinical features:

- ❖ As we said lymphoma and leukemia affect the immune system, so these patient will have **derangement in immune system** (hypogammaglobulinemia; which means that the immune system doesn't produce enough amount of immunoglobulins and patients will be immunosuppressed) and also they will suffer from **hemolytic anemia** (cold type autoimmune hemolytic anemia, as you remember).
- ❖ Patient will have **indolent** and **mild** course (indolent is opposite to aggressive), and **stays for years**, the patient has no symptoms and the disease will be discovered **incidentally** {they have no symptoms so during measuring of blood count, large number of lymphocytes will be noticed}, because these lymphocytes are proliferating slowly but they have long half life (the mitosis is very slow), so they will not be affected by chemotherapy. So no treatment is given unless the symptoms appear and the case become more progressive.**{Chemotherapy work on mitotically active cells}**

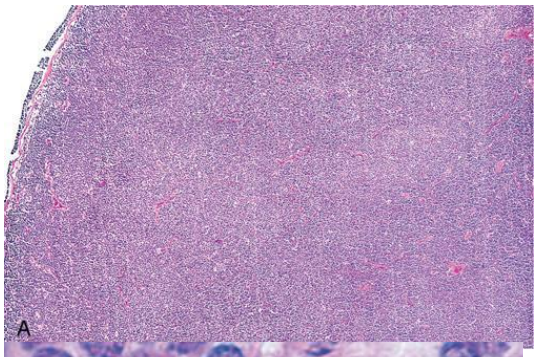
Written by سلسبيلا فاروق بني حمد

- After a long period of time, cells will gain more mutations and become more progressive, so 10% of cases of CLL will transform to high-grade lymphoma.

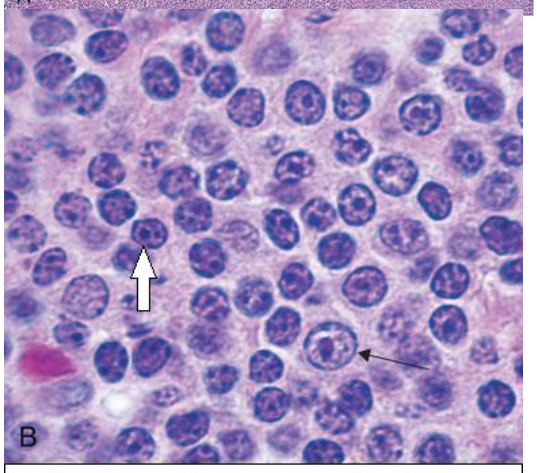
Morphology:

1) In the lymph nodes:

A: Low-power view, we see **diffuse effacement** of nodal architecture, so the lymph node will appear like a solid mass; you can't distinguish cortex from paracortex and you will not have germinal centers.



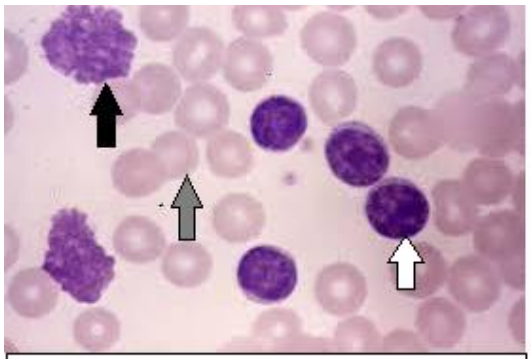
B: At higher magnification, the **majority** of the tumor cells have the appearance of **small**, **round**, **dark** lymphocytes, with scattered larger cells called **prolymphocyte** (it is earlier stage of development of lymphocyte), that have a **central nucleolus**, this is the view in the early stages of the disease. While when the disease become more **progressive** the majority of the tumor cells will be **prolymphocyte**, larger than lymphocyte, also they have faster replication and this make the disease **progress faster**.



The white arrow represents a lymphocytes
The black arrow represents a prolymphocyte

2) In the peripheral blood:

We can see large number of lymphocytes that are **mature** and **small** and you see **dead cells** that are called **smudge** (burst, destroyed), and this means that these lymphocytes are **fragile** and we will notice **high level of LDH** (as in hemolytic anemia) in blood as well. If we want to compare lymphocyte with lymphoblast, we will see that the size of the nucleus of lymphocyte is almost similar to RBC and its color is dark while it is pale in lymphoblast and larger in size.



White arrow >> lymphocyte
Black arrow >> smudged (burst) cell
Grey arrow >> RBC

Written by سلسبيلا فاروق بني حمد

3) Follicular Lymphoma:

- Most common lymphoma in the western countries.
- Affects elderly.
- Arises from germinal centre of B-cells, this is why it is called follicular.
- It is **low-grade** B-cell lymphoma, cells have mutations and they undergo proliferation, but still they are **mature** and can **do some of its normal function** so the shape of follicles is normal. When we look under the microscope we will see **large** lymph nodes and filled with germinal centers this is why it is low grade and thus has the ability to do its function.

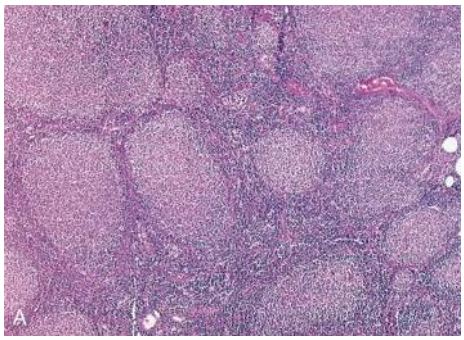
- Lymphoma cells have specific translocation between chromosome 14 and chromosome 18, **t(14:18)** .
  - Bcl-2 (anti-apoptotic protein, prevent cell death) locates on chromosome 18.
  - Immunoglobulin heavy chain (IgH) locates on chromosome 14, and it is very active in B lymphocytes because they synthesize immunoglobulins continuously.
  - In follicular lymphoma, Bcl-2 gene translocates and fuses with IgH gene on chromosome 14, so in each replication there will be an extra copy of Bcl-2 protien (overexpression of Bcl-2) which lead to increase cell life and so formation of the tumor.

Clinical features:

- Patient has generalized lymphadenopathy, which means enlargement of lymph nodes, but it is **generalized**; it is a low-grade and proliferate very slowly, so the neoplastic cells will present in **multiple** lymph nodes and the patient will go to the clinic suffering from enlargement of multiple lymph nodes (axillary, inguinal, abdominal, chest…etc.), this is an **important characteristic feature of follicular lymphoma**.
- **Histologically**: Lymphoma cells proliferate to form abnormal, large, crowded follicles.
- Patients have indolent course (again, because it is a low-grade tumor), transforms into high grade lymphoma in **40%** of cases {tendency of transformation from low-grade into high-grade tumor is more in follicular lymphoma than in CLL).

Written by سلسبيلا فاروق بني حمد

Morphology:

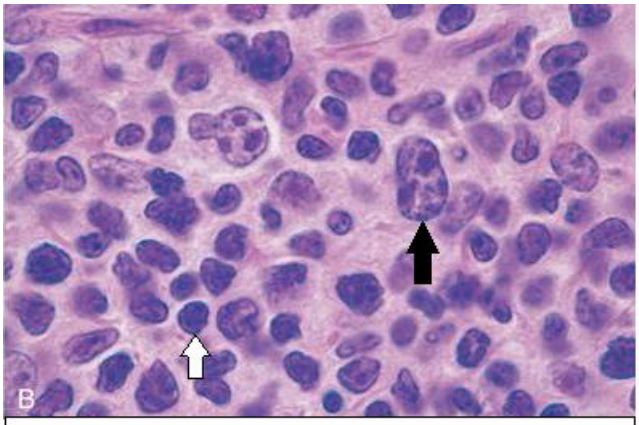


A: **Large** lymph node filled with follicles, the cells arise from germinal centers and form follicles with **normal** shape but they are **large** in size.

B: At high magnification, There are two types of cells;

1) **Small irregular** (**cleaved**) **dark** cells, called **centrocytes** (centro means from germinal center, and –cyte means mature).
   (cells are irregular in shape not round because they are in the germinal centre and still not fully mature)--- **important**

2) **Large** cells, called **centroblasts** (-blast means immature and so they are larger in size).



White arrow >>Small irregular (cleaved) dark cells, called centrocytes
Black arrow >> Large cells, called centroblasts

❖ In transformation the predominant cells are **Large immature cells**, always keep in mind that the less the maturity the worse the case, because they progress faster and don't respond to treatment.

❖ **How to differentiate between follicular lymphoma and reactive follicular hyperplasia (that we talked about previously)?**

✓ In both of them, under the microscope we see crowded and large germinal centers.

✓ So in order to differentiate, we use **special stain for Bcl-2**, the cells of follicular lymphoma will be very bright after staining which means the cells are expressing Bcl-2 in large amount, while in reactive follicular hyperplasia the result will be negative which means the amount of Bcl-2 is normal.

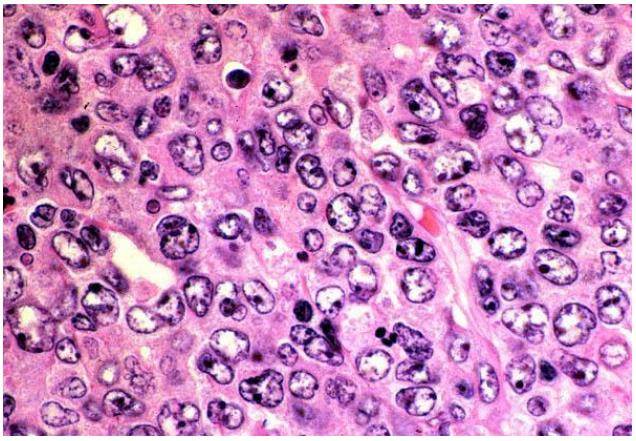
Written by سلسبيلا فاروق بني حمد

4) Diffuse Large B Cell Lymphoma:

- **Diffuse** and **large**, this means it is definitely **high-grade**. As we know, lymphocytes are the smallest nucleated cells in the body but in this lymphoma they are very large, so it is an **aggressive high-grade** lymphoma.
- Most common type of lymphoma in **adults** {follicular lymphoma is the most common type in west, but in our region and in the rest of the world except the west, diffuse large B cell lymphoma is the most common in adults} , accounting for approximately 50% of adult Non-Hodgkin Lymphomas (NHLs) , also can arise in children but most common in adult.
- Cause:
  - **In most cases**, this lymphoma arises **de novo**; idiopathic, without previous cause.
  - **In minority,** it arises as a transformation from low grade B-cell lymphoma (from CLL or Follicular lymphoma).

- High-grade lymphoma, progressive and fatal if not treated, this type of lymphoma respond well to chemotherapy because the cells proliferate fast, so they will be killed as a result of using chemotherapy, this is not the case in low-grade tumor because using chemotherapy with them will kill only 10% of the malignant cells as they are proliferating slowly and not mitotically active so the chemotherapy won't affect them.

Morphology:



- The cells are **very large** (their size is at least double of the size of normal lymphocytes) and hence that's why we call it diffuse **large** B-cell lymphoma.
- The **architecture is lost**, you can't recognize follicles or paracortex area, so there is **effacement** and if you go to a higher magnification you will see large cells.
- Tumor cells have large nuclei, and nucleoli are very prominent because the nucleus is very active.

Written by سلسبيلا فاروق بني حمد

5) Burkitt Lymphoma:

- **High-grade B-cell lymphoma**.
- Most common in **children**.
- Was discovered by Denis Parsons **Burkitt**, a surgeon who was living in Africa, and he noticed that there are many children have enlargement in the jaw and after examining under the microscope he discovered that there is a lymphoma and so it was named **Burkitt lymphoma**.
- It is endemic in Africa and occur sporadically (individual cases) worldwide.
- This disease has multiple phases, in Africa it is very common because they have high **EBV (Epstein-Barr virus)** infection which is endemic in Africa, and nearly 100% of Burkitt lymphoma patients have EBV. But in the rest of the world, this lymphoma occurs in individual cases.

❖ **This lymphoma occur because of specific translocation t(8:14):**
- Again, chromosome 14 has IgH gene which is very active in B--cells.
- Myc gene located on chromosome 8.
- In Burkitt lymphoma MYC gene translocates and fuses with IgH on chromosome 14, so in each replication there will be an extra copy of MYC protein, which activates other transcription factors and causes continuous cell proliferation. Also the cells are proliferating very fast so they are aggressive so **this is the fastest tumor in human** and the doubling time is about 8 hours; so after 8 hours the tumor size will be doubled.

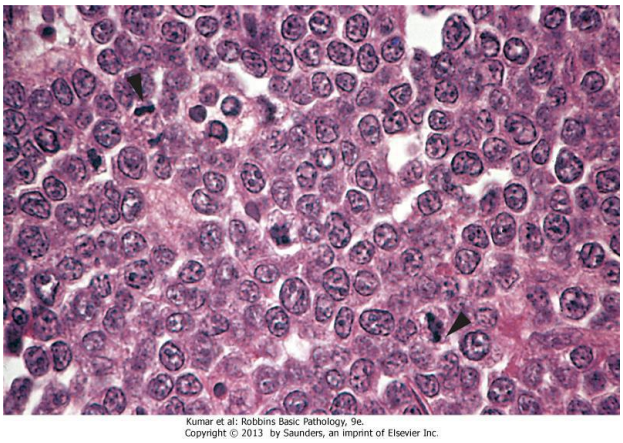
❖ **Important manifest of this lymphoma**, it tends to go outside of the lymph nodes (rarely arises in lymph nodes), so it arises in extranodal sites (mostly in the jaw, where viruses enter the body, and in terminal ileum).

❖ Lymphoma is rapidly growing and fatal if not treated (high grade lymphoma).

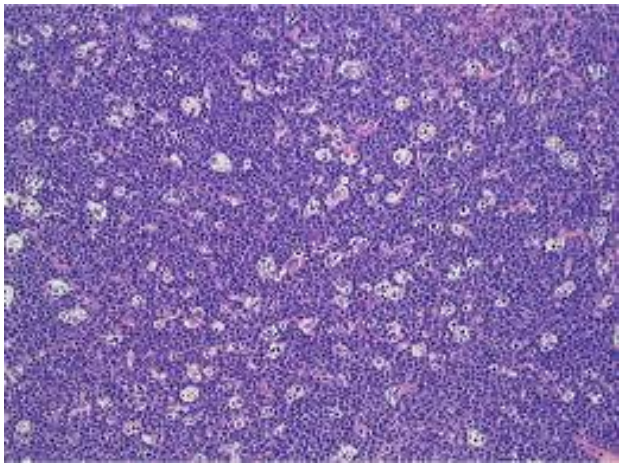
Written by سلسبيلا فاروق بني حمد

Morphology:

- The cells are **round, intermediate** in size (in contrast to the diffuse large B-cell lymphoma) and **monomorphic**; all the cells have the same morphology (which is different from the small lymphocytic lymphoma).
- **{**The **tumor cells and their nuclei are fairly uniform, giving a monotonous appearance}** **Important**
- Arrowheads in the picture represent the mitotic activity.



- As it is aggressive type, we can see a lot of mitosis and apoptosis. When the cells die by apoptosis, macrophages will engulf them, so we can see large number of macrophages between the malignant cells. This morphology is described as "**starry sky**", like if you are looking to the sky at night and you see stars, stars (the white dots in the picture) are the macrophages which engulf dead malignant cells.



- By this, we finished talking about non-Hodgkin lymphomas.
- The rest of the sheet is only revision.

Good Luck
- Salsabeela BaniHamad

Written by سلسبيلا فاروق بني حمد

Revision:

- All Lymphocytes that are mentioned in this lecture arise from B-cells except ALL which arises from T-cells

<table>
<tr><th>Lymphoma</th><th>Description</th></tr>
<tr><td>1) Acute Lymphoblastic Leukemia/ Lymphoma (ALL):</td><td>

Arises from immature cells (-blastic)
high-grade
Arise from both bone marrow and lymph nodes (either from B or T cells).
Two types:
<table>
<tr><td>B- ALL</td><td>T- ALL</td></tr>
<tr><td>more common</td><td>less common</td></tr>
<tr><td>Most common cancer in children</td><td>Occur at adolescence age and most common in boys</td></tr>
<tr><td>Arises from BM</td><td>arises from the thymus</td></tr>
<tr><td colspan="2">Circulate in blood, can affect LNs and solid organs</td></tr>
</table>

Lymphoblasts exceed 20% and lead to myelopthistic anemia
Clinical features: Abrupt, stormy onset of symptoms /fever /Fatigue and tiredness/Bleeding/ Bone Pain.
Disseminate to other tissues: lymphadenopathy/ Splenomegaly/brain and testicular involvement.
Morphology: large lymphoblasts with large number, nucleus is dark with no nucleoli/ minimal agranular cytoplasm

</td></tr>
<tr><td>2) Chronic Lymphocytic Leukemia/ Small Lymphocytic Lymphoma (CLL):</td><td>

malignant cell is lymphocyte
Arise from both bone marrow and lymph nodes (from B cell only).
Low-grade tumor.
Cause: Bcl-2 is increased (up-regulated) which means the cells will have longer life and persist for a longer time.
Most common in elderly (doesn't appear in children).
Clinical features: derangement in immune system (hypogammaglobulinemia)/ hemolytic anemia/ indolent and mild course/stays for years and discovered incidentally.
Not affected by chemotherapy because the mitosis is very slow.
10% will transform to high-grade lymphoma.
Morphology:

in lymph nodes: diffuse effacement, in larger magnification we see the majority are small, round, dark lymphocytes with scattered larger cells called prolymphocyte, when transformed to high-stage prolymphocyte number will increase.
In peripheral blood: large number of mature and small lymphocytes and dead cells that are called smudge + increase in LDH.

</td></tr>
<tr><td>3) Follicular Lymphoma:</td><td>

Most common lymphoma in the west.
Affects elderly.
Arises from germinal centre of B-cells only.
low-grade
Cause: t(14:18) , Bcl-2 gene (present normally at chr18) translocates and fuses with IgH gene on chr14 which lead to overexpression of Bcl-2 and increase cell life.
Clinical features: generalized lymphadenopathy in multiple lymph nodes/

</td></tr>
</table>

Written by سلسبيلا فاروق بني حمد

	indolent course. • transforms into high grade lymphoma in 40% of cases • **Morphology**: abnormal, large, crowded follicles, at high power we see two types of cells: 1. **Centrocytes;** Small irregular (cleaved) dark cells. 2. **Centroblasts;** immature large cells.
4) Diffuse Large B Cell Lymphoma:	• Arises from B-cells. • Diffuse and large, this means it is definitely **high-grade** • Most common type of lymphoma in adults worldwide, accounting for approximately 50% of adult Non-Hodgkin Lymphomas. • Causes: de novo in most cases, **In minority,** it arises as a transformation from low grade B-cell lymphoma • respond well to chemotherapy because the cells proliferate fast • Morphology: cells are **very large**, **architecture is lost** (**effacement**), Tumor cells have large nuclei, and nucleoli are very prominent.
5) Burkitt Lymphoma:	• **High-grade B-cell lymphoma**. • Most common in **children**. • endemic in Africa and occur sporadically (individual cases) worldwide. • High association with EBV • **Cause: t(8:14),** myc gene (which present normally on chr 4) translocates and fuses with IgH on chr 14 , lead to increase myc which activates other transcription factors and causes continuous cell proliferation • **The fastest tumor in human**, doubling time is 8h. • Arises in extranodal sites (mostly in jaw and terminal ileum). • Rapidly growing and fatal if not treated • **Morphology**: ▪ **round, intermediate** in size and **monomorphic** ▪ you can see a lot of mitosis and apoptosis and so large number of macrophages between the malignant cells This morphology is described as "**starry sky**".

☺ GOOD LUCK ☺

Written by سلسبيلا فاروق بني حمد