Sheet No. 7

PATHOLOGY

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Neoplastic proliferation of WBCs:

General Information:

- Mostly considered malignant [**No benign lymphomas**]
- Fluid tumors, in contrast to most cancers in the body [called solid tumors] *many of them circulate in the blood (they don't form a mass).
- They differ in their biological behavior. Cancer is a group of diseases not a single disease, so we'll find tumours ranging from indolent (low grade slowly growing) to very aggressive in the same main group of cancers.
- Common cancers, in adults they're the third or fourth most common cancer and **in pediatrics they're THE most common**
- Current classification system: World Health Organization (WHO) classification system for Hematolymphoid neoplasms which is the most advancing one.

➲ Previously, classification depended on the morphology, now we incorporate more tests into classification like tests based on morphology, protein and molecular tests which created an advancement.

➲ Classified according to lineage into: myeloid vs lymphoid vs histiocytic. lymphoid has B vs T cell types.

Lymphoma:

➲ Malignant Neoplasm of lymphocytes (No benign lymphoma)

➲ Called:

- lymphoid leukemia if it affects the peripheral blood or BM.
- lymphoma if it affects lymph nodes or solid organs (1/3 of cases are extranodal lymphoma) **We already know that lymphoid cells don't only reside in the lymph nodes.**

➲ Lymphomas are Classified into 2 main categories: Hodgkin and non-Hodgkin lymphoma

- Non-Hodgkin lymphoma is classified into B and T-cell lymphoma
  - **B-cell lymphomas are more common** since the immune System is dynamic and involves continuous immunoglobulin synthesis, so, accidents during class-switching can happen in the Immunoglobulin gene which cause mutations to be more probable in B cells than in T-cells) *T-cells have a more stable genome

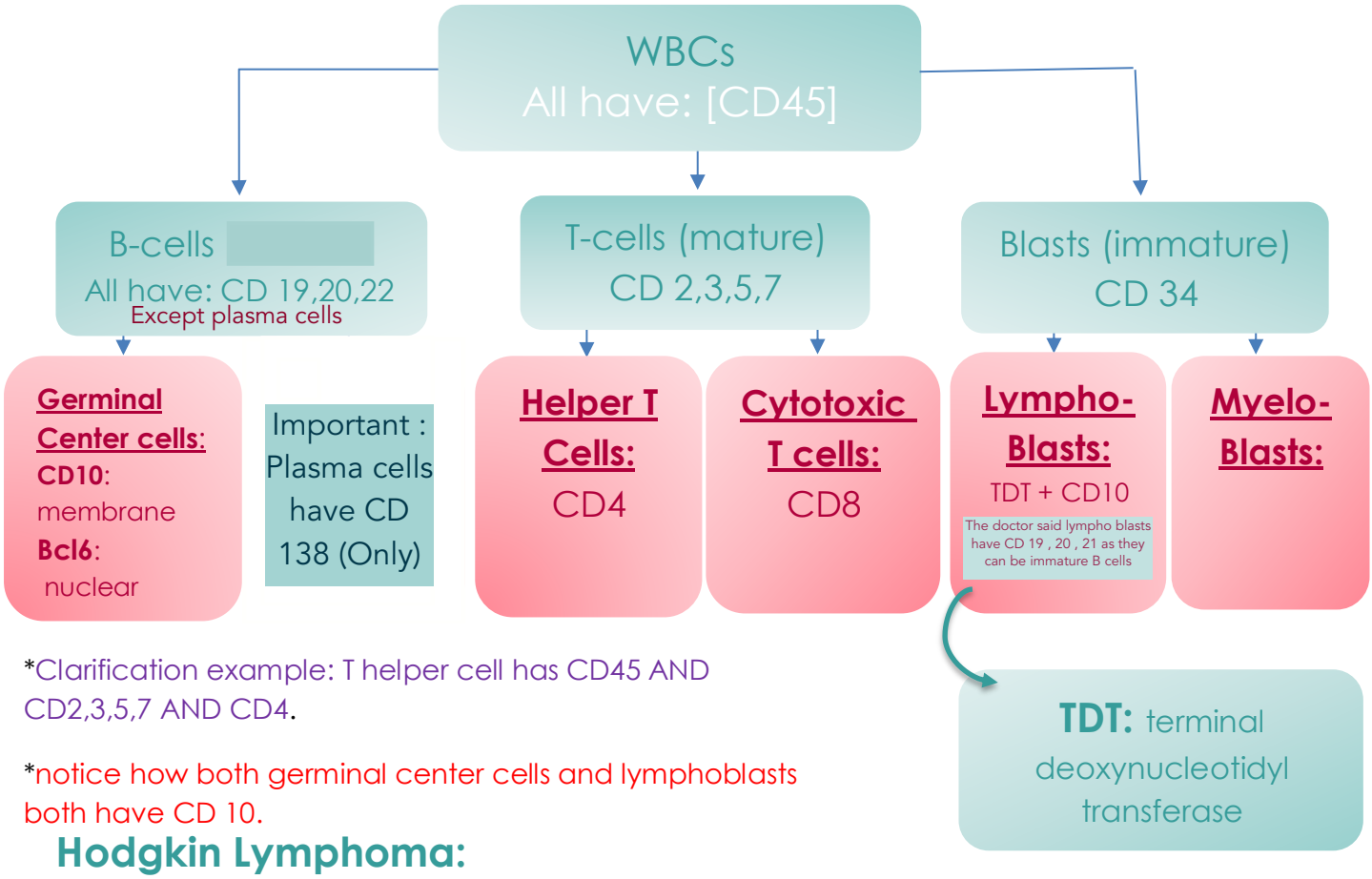
➲ All are malignant, but can be of low-grade (indolent) which persists for a long time or high-grade (aggressive) which causes death faster.

➲ Diagnosis is made through examination of a biopsy by pathologists first, morphologic examination is done to see the tissue in general and then, immunophenotypic tests to discriminate the T and B types which include: immunohistochemistry- solid paraffin blocked tissue sections- or flow cytometry for fluids- Blood or BM.

› Sometimes a test for mutations is performed for confirmation

➲ **Immunodeficiency is a risk factor for lymphoma, and vice versa**

◆ Commonly tested markers for Immunophenotypes: (you have to know all of these)



*Clarification example: T helper cell has CD45 AND CD2,3,5,7 AND CD4.

*notice how both germinal center cells and lymphoblasts both have CD 10.

Hodgkin Lymphoma:

➲ Constitutes 30-40% of all lymphomas
  › Although NHL constitutes 60%, its subtypes vary a lot from each other.

➲ **Most common type of lymphoma in Jordan**
  › most common in children and young adults
  › In adults: non-Hodgkin is more common

➲ unique characteristics that make it different:
  › The neoplastic cells are **giant** [originally, lymphocytes are the smallest nucleated cells in the body]
  › have different morphology and immunophenotype from normal lymphocytes.

*The number of neoplastic cells forms less than 10% of tumor mass (only few and dispersed), while the rest are normal inflammatory cells.

- Arises primarily in a localized area of lymph nodes [most commonly in the lower neck lymph nodes, axilla, mediastinum] then spreads to anatomically adjacent LN group (predictable spread, neck→ axilla → mediastinal LN → visceral LN in the abdomen then spleen and BM) unlike cancers in general.

- Mesenteric LNs and Waldeyer's ring (oral and nasal cavity) are rarely involved
  - Lymphoma here → probably NHL (Non-Hodgkin Lymphoma)

- Bimodal age distribution (first peak in children, then in old age groups)
  *generally in cancers there is one peak age that the cancer happens most commonly at.
- B-symptoms: patients commonly have fever, night sweats and weight loss which are common with chronic infection diseases

Hodgkin lymphoma is a homogenous cancer, it has many subtypes that are very similar.

Story Time:

In the past, H. lymphoma was believed to be a disease because of the previously mentioned symptoms, not a neoplastic condition.

- Classification:
  - Classic Hodgkin lymphoma (95%):
    4 subtypes:

i. Nodular sclerosis → **most common type all over**
ii. mixed cellularity
iii. lymphocyte-rich we see lymphocytes with the giant cells
iv. lymphocyte-depleted we see histiocytes in large number

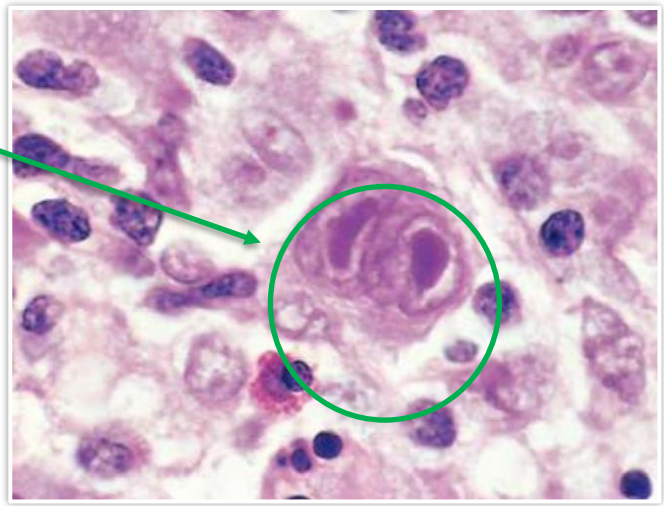
Rare

In the first two, normal inflammatory cells make the bulk of the tumor [WBCs]

  - Non-Classic Hodgkin lymphoma (5%): Nodular lymphocyte-predominant [LP]

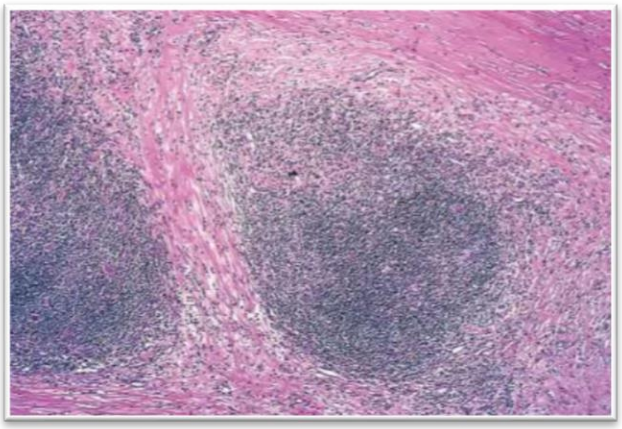
Predominant doesn't equal rich

Reed-Sternberg cells (RS): bi or multi-nucleated giant cell, prominent nucleoli that's the size of a whole normal cell! abundant cytoplasm with eosinophilic nuclei. Compare the size with cells around it.



Hodgkin cells: mononuclear giant cell (single nucleus)

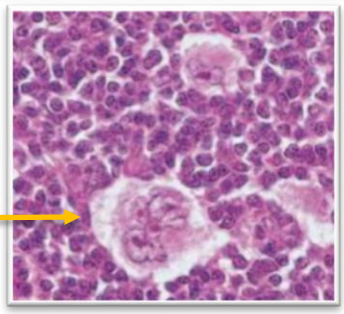
- These cells differ in morphology AND immunophenotype from lymphocytes, They Both express CD30 and CD15 which are normally absent but get expressed through the pathogenesis. They don't express CD20, CD3 and CD45, and this is why it took a very long time until it was recognized as a neoplastic B-cell (it was thought as an inflammatory cell).
- *Hodgkin described the clinical view, and R-S discovered the histological morphology*



- Nodular Sclerosis HL: **the most common**

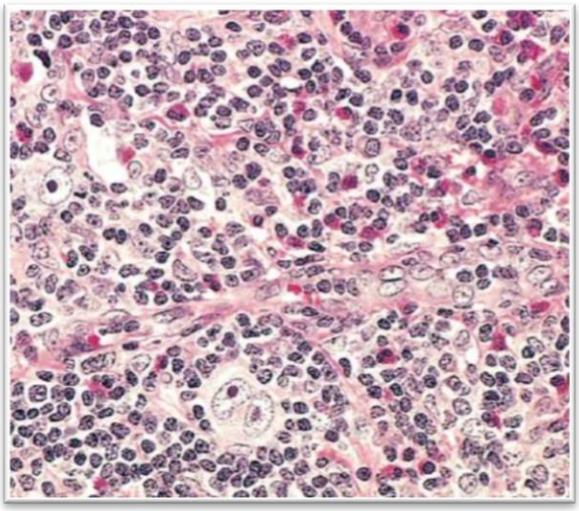
Morphology: the lymph node has nodules with dense sclerosis (fibrous bands) that separates these nodules from each other

Why? The neoplastic cells activate fibroblasts to produce collagen which gives this architecture at the end.



- Common in children and young adults [first HL peak]
- RS cells in nodular sclerosis show a clear cytoplasm, as a retraction artifact from formalin, called Lacunar cells.

- Mixed cellularity HL



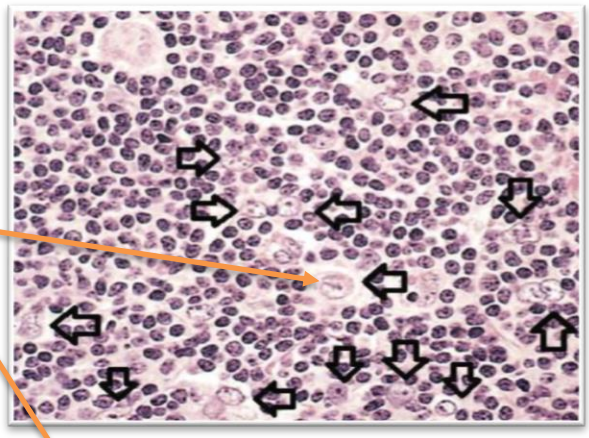
Morphology: few neoplastic cells with a background filled with lymphocytes and reddish eosinophils.

Reason for eosinophilia? RS cells produce cytokines that bring all these inflammatory cells.

- Common in old people [second HL peak]
- Numerous RS cells (I know it says few above, few is compared to the background cells)
- Lacks fibrous bands→ **diffuse area with numerous RS cells with a background of inflammatory cells [**mixed neutrophils, eosinophils, lymphocytes, plasma cells and histiocytes**]**
- Associated with EBV with high percentage

◆ Non-classic lymphocyte-predominant HL:

High power view, we can't see the nodular architecture anymore

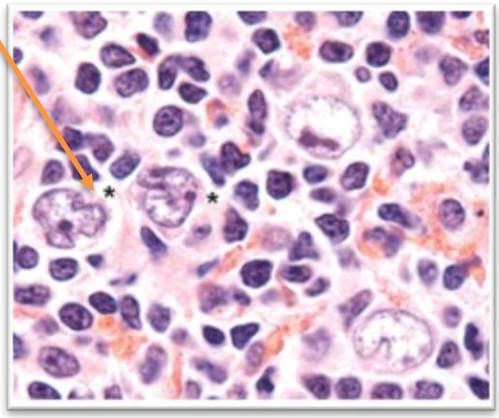


Malignant cells different in their morphology than the ones before, called lymphohistiocyte (L&H) variant RS cell [in text-books] but simply called LP cells in clinical practice.

↳ Cells Resemble popcorn (popcorn cells)

› Giant cell with **multi-lobulated** (not multi nucleated like RS) vesicular (which means **white** nucleus and small blue nucleoli).

Immunophenotype: **Express normal B-cell markers** (CD45, CD20), negative for CD30 and CD15 which are markers of **classic HL**



➲ Background of lymphocytes, arranged in nodules but no fibrous septa, very large follicles filling the lymph node so it gives the architecture of a lobule.

➲ Excellent prognosis, better than the classic HL :D

◆ Pathogenesis and outcome of HL:

➲ Neoplastic cells originate from germinal center B-cells but they are VERY different from them

› Frequent association with EBV → mixed cellularity is the most common one

› RS cells secrete IL-5, chemoattractant for **eosinophils** → causing eosinophilia in the blood in severe cases

› Also secrete IL-13 and transforming growth-B (TGF-ß) which activate themselves [autocrine effect] and other RS cells supporting their survival.

› Express programmed death (PD) ligands on the surface of RS, which antagonize T-cell response by binding to them causing their apoptosis, escaping immune surveillance

↳ In therapy now we use an antibody that binds these PD ligands so the lymphocytes can act as natural fighters of the cancer

➲ Prognosis is generally good, it wasn't until the 70s that they found a regiment of chemo and radio therapy for the treatment of HL with a good response rate

NON-Hodgkin Lymphoma:

Divided into B and T lymphomas and the B is more common

1. Diffuse large B-cell lymphoma [DLBCL]

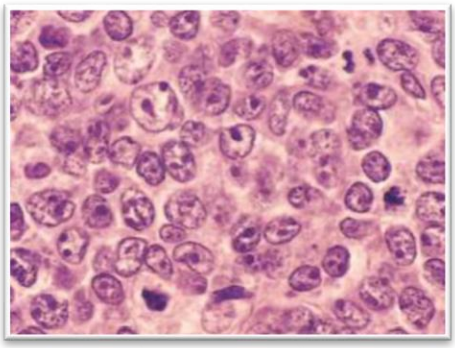
Most common NHL

- Predominantly in **adults**
- High-grade (rapidly growing mass) and doesn't get treated usually → fatal
- Most common non-cutaneous **extranodal lymphoma** (GI most common)
- Mutations: (this lymphoma is heterogenous)
  - 2/3 have activating mutation of **Bcl6 promotor gene** → which is an important regulator of gene expression in germinal center B-cells (so it would be present in B-cells in the germinal center phase- go back to page 2- marker tests)
    - ↳ when this is mutant it upregulates the proliferation of B-lymphocytes.
  - **30%** have t(14;18) (Bcl2→ IgH) [translocation of Bcl2 gene from ch.18 to ch.14, which affects its expression rate]
    [Note: **IgH** is very active because it produces the heavy chain of Igs]
    - ↳ Bcl2 gene fuses with the IgH on chromosome 14, so with every transcript of IgH, we have Bcl2 being expressed which results in overexpression of Bcl2 protein (an anti-apoptotic protein) so it prolongs the cell survival.
  - Few has mutation in **MYC gene** [the MYC product activates the cell cycle]

Morphology/ light microscope:

↳ **relate the NAME with the malignancy properties of cells**

Under low power: you'll see **Diffuse Cells** and disrupted and effaced architecture of the normal lymphoid tissue (no follicles or sinuses).



High power: you'll see that cells are abnormally LARGE (up to 3x normal lymphocytes)

- Irregular nuclei (they have small prominent nucleoli which means that the nucleus is very active).
- frequent mitosis and apoptosis, features of malignancy.
- Positive for CD20 a B-cell marker [indicating the origin]

Subtypes of DLBCL:

i. Most cases arises DE NOVO, some complicate a previous low-grade B-cell lymphoma

ii. Secondary DLBCL: it arises from **low grade B cell lymphoma** gaining additional mutations

iii. Primary mediastinal large B- cell lymphoma

In the thymus -which is located in the anterior mediastinum- we have few B- cells, if they get mutated this lymphoma will develop.

- Mutations in this subtype differ from the nodal or GI DLBCL
- Most patients affected are [middle aged] women (F> M)
  - ↳ THE only one that's more common in women.
- It disseminates to distal visceral organs or to CNS [characteristic of this subtype]

iv. EBV- associated DLBCL:

- It arises in elderly and immunosuppressant patients
- Infection with EBV will lead to **normal polyclonal B- cell proliferation**, then if multiple mutations are added this lymphoma will develop
- Prognosis is BAD ☹

v. human herpes virus-8 DLBCL:

- Etiology: Infection of B- cells by HHV-8 can lead to this lymphoma, as HHV-8 encodes for CYCLIN D1 MIMICKER PROTEIN, which in turn keeps the cell cycle ON by alternating the cell phase from G1 phase to S phase.
- common in immunosuppressant patients
- other name for this subtype is primary effusion lymphoma [causes pleural effusion] it appears in plueral cavity by accumulating a fluid that is filled with malignant B-lymphocytes which test +ve for HHV-8 [characteristic for this subtype]

Human herpes virus-8 (HHV-8) :

This virus is an oncogene, it causes **KAPOSI SARCOMA** which is a neoplasm of blood vessels

Follicular lymphoma:

- Second most common NHL
- Common in the West (less in Asian countries)
- Mainly in > 50 years [old people] AND in M>F
- Patients present with generalized lymphadenopathy (lymph node enlargement in most of the body)
- Commonly disseminates to BM, liver and spleen (80%), but it's still a low grade lymphoma

*Lymphomas are more common in **males** than females*

Primary Exception: - mediastinal large B-cell lymphoma

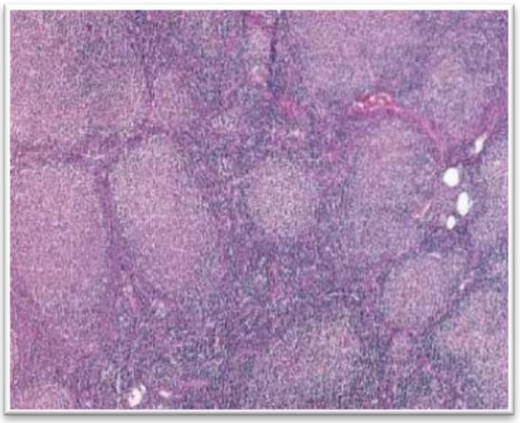
Paradoxically, low grade lymphoma easily disseminates but doesn't kill the patient (they have a longer time so you can see them in different areas of the body), on the other hand, DLBCL starts at a certain area and destroys very fast.

Pathogenesis:

- t(14;18) (Bcl2→IgH): described earlier, which will lead to Overexpression of Bcl2 resulting in prolonged survival of lymphoma cells → this mutation is found in all follicular lymphomas
- 1/3 of patients have mutations in genes encoding histone-modifying proteins (epigenetic change, not in nucleotides)

Morphology: remember the name

The normal architecture of the lymph node is effaced by **nodular proliferation** that form follicles.

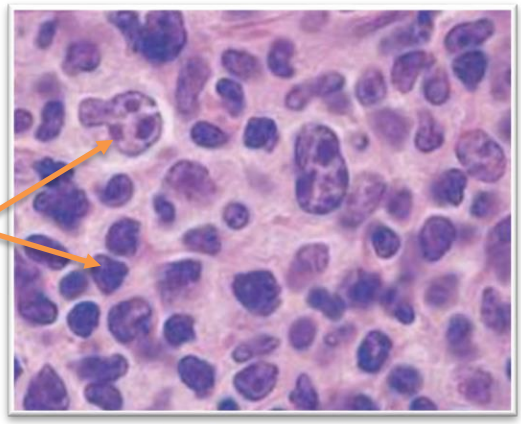


Note: remember! Reactive follicular hyperplasia is a benign case in which B cells proliferate in association with rheumatological diseases, HIV, toxoplasmosis.

- In this hyperplasia we DON'T have disrupted or effaced architecture

BUT, in **follicular lymphoma** the architecture is effaced by crowded follicles hitting each other and fusing, with variant follicle sizes (small, large, fused follicles and so on)

Zooming into the follicles we see 2 population of cells:



centrocytes: small, dark irregular [old name was cleaved lymphocytes] *cyte- mature cells*

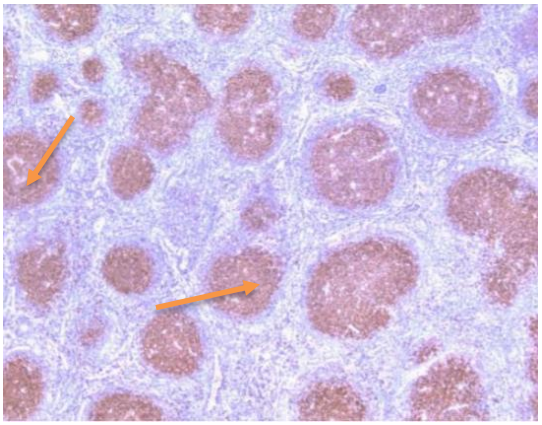
centroblasts: large lymphocytes with vesicular nuclei and small nucleoli *blast- immature*
-More proliferating than cytes.

Cenrtro-: because they're in the germinal center.

➲ In most cases (early stage) the centrocytes predominate (so in most cases, it is a low-grade lymphoma). With time, centroblasts increase and the disease becomes high grade resembling DLBCL.

- These cells are Germinal center cells [B cells] so they express CD20, CD10, Bcl6 and Bcl2 is +ve due to the mutation.

- We can differentiate between **malignant follicular lymphoma (Bcl2 +ve)** and benign reactive follicular hyperplasia (Bcl2 –ve) by Bcl2 immunohistochemical stain. If the follicle is Bcl2 stain +ve it means malignancy and FL.



Prognosis:

- Indolent course
- Conventional chemotherapy is ineffective in the early stage (as these cells are slowly proliferating, mitosis is low and most of the tumor cells are not affected by chemo drugs targeting proliferation)
  - ➔ 40% develop transformation to DLBCL (unfortunately, the prognosis gets worse than de novo DLBCL)
- Overall median survival is 10 years
- If the disease turned to the high state -in which proliferation is accelerated, Therapy is reserved to these symptomatic patients, with bulky tumors or transformation into DLBCL.
  THEN WE USE cytotoxic chemotherapy,
  - Drugs:
- Monoclonal antibodies “anti-CD20” that target all B cells- neoplastic and normal ones
- anti-Bcl2 that targets neoplastic cells.

Good Luck