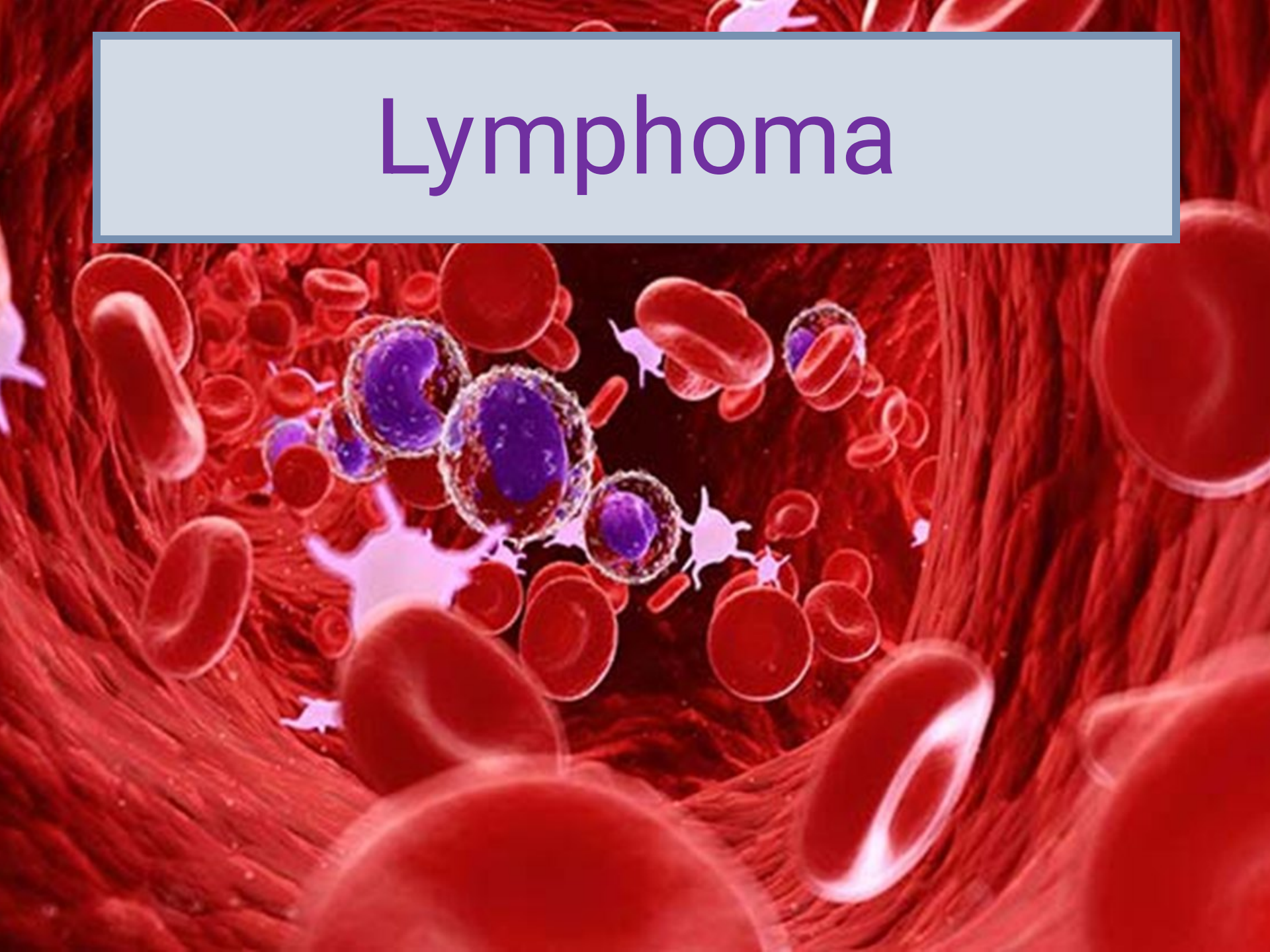


Lymphoma



Leukemia vs lymphoma

Presentation

HL VS NHL

Prevelence

Age

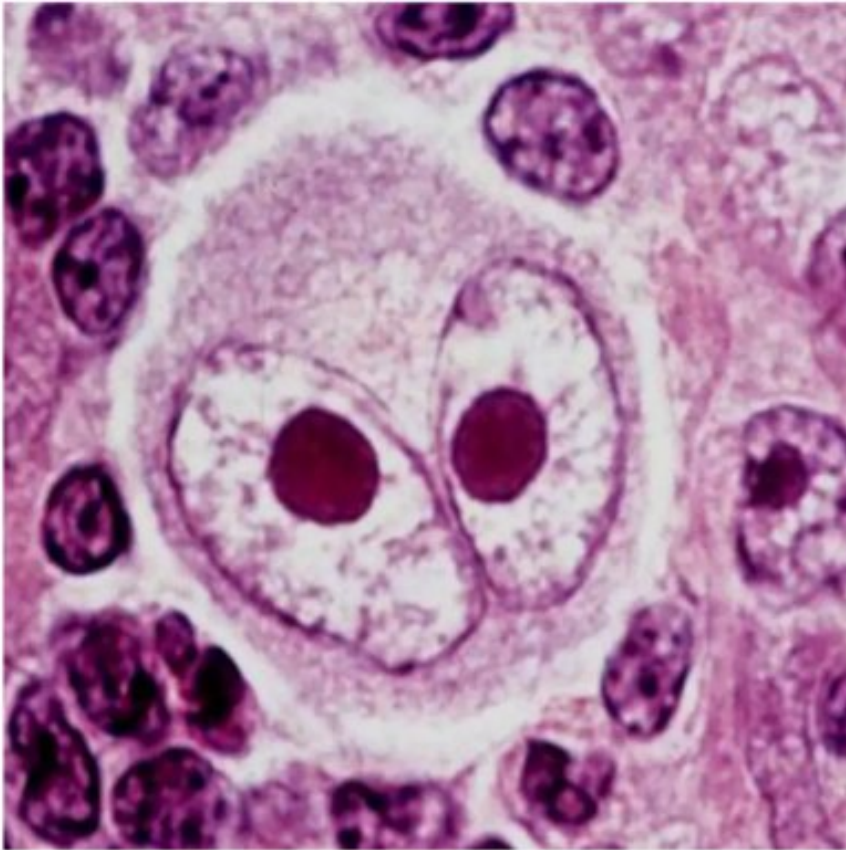
Cell of origin

Malignant cells

Nodal vs extranodal

B symptoms

“Reed-Sternberg cell”



Non-Hodgkin lymphoma

More prevalent

Lymphoid cells

Not prognostic

diffuse

Often multiple nodes

common

common

Occurs

Limited indications

Hodgkin lymphoma

Less prevalent

Reed Sternburg cells

inflammatory cells

outnumber the tumor
cells

Prognostic

Contiguous

More often localized

rare

uncommon

Not happened

Radiation is important
part of treatment.

Prevalence

Malignant cell

B- symptoms

spread

Mesenteric LN,
Waldeyer ring

Extranodal
involvement

Leukemic phase

Radiotherapy

Diagnosis

- Bx LN
- Immunohistologic stains
- Flow cytometry
- FISH
- Molecular testing

Immune profile

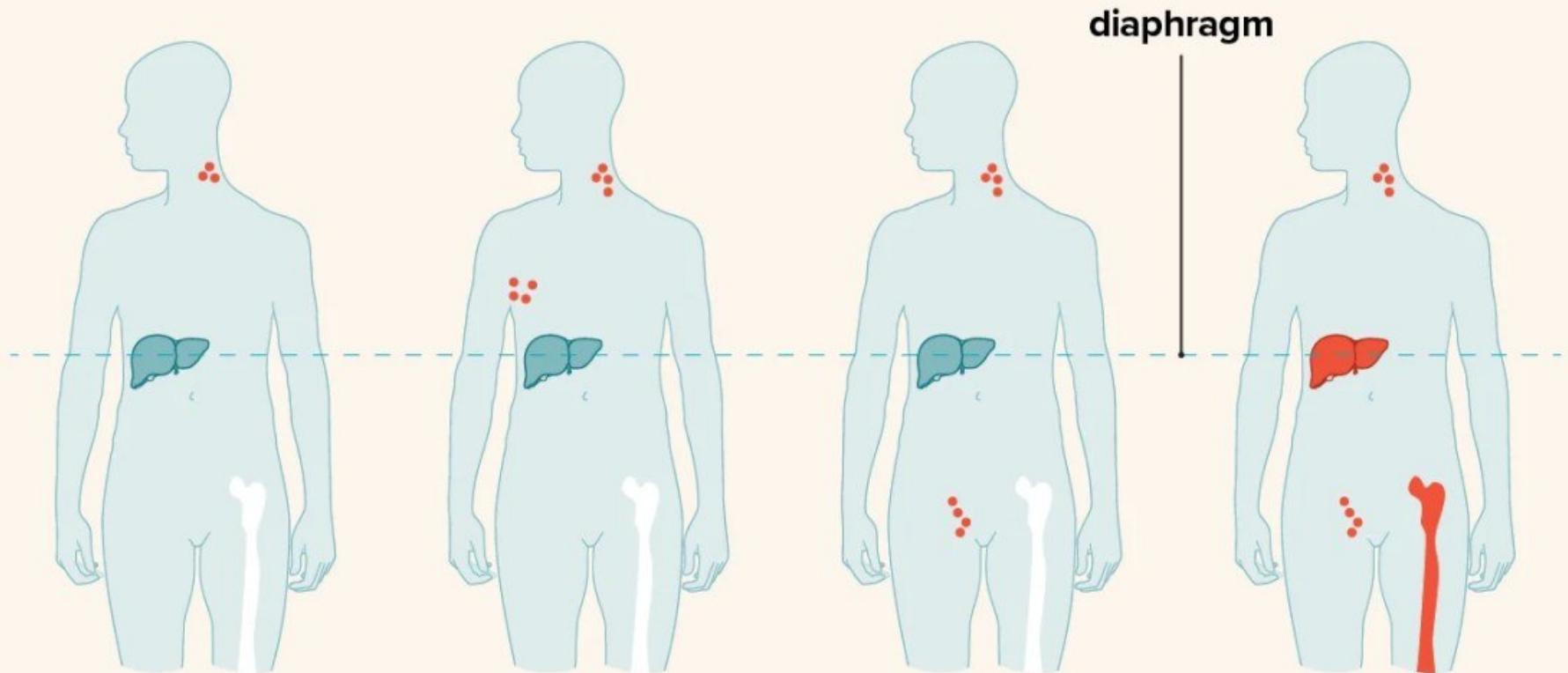
- TdT – B or T cell precursor marker
- CD45 – lymphocyte common antigen B and T
- CD3 – all T lymphocytes
- CD4- T helper
- CD8 – T cytotoxic
- CD 19 CD 20 – common B lymphocyte
- CD10 BCL 6 – B lymphocyte in germinal center

Staging

The clinical stage is the most important prognostic indicator.

- Physical examination
- CT scan of neck chest abdomen pelvis
- Bone marrow biopsy
- PET scan (dx or follow up) – persistent masses on ct after treatment (residual lymphoma – fibrous scar tissue)

Stages of Non-Hodgkin's Lymphoma



stage 1:

localized disease;
single lymph node
region or single organ

stage 2:

two or more lymph
node regions on the
same side of the
diaphragm

stage 3:

two or more lymph
node regions above
and below the
diaphragm

stage 4:

widespread disease;
multiple organs, with
or without lymph node
involvement

Lymphoma

Hodgkin lymphoma

Classical HL

- Nodular sclerosis
- Mixed cellularity
- Lymphocyte rich
- Lymphocyte depleted

Nodular Lymphocyte predominant HL

Non Hodgkin lymphoma

B/T-cell Lymphoblastic
lymphoma/ALL

Peripheral NH Lymphoma

B-cell NHL

SLL/CLL

Follicular lymphoma

Mantle cell lymphoma

Marginal zone lymphoma

DLBL

Burkitt Lymphoma

Low
grade

High
grade

T-Cell NHL

Mycosis fungoides/Sézary
syndrome

Peripheral T cell lymphoma

ALCL

High grade vs low grade NHL

Aggressive NHL

- short natural history (patients die within months if untreated)
- disease of rapid cellular proliferation
- Potentially curable with chemotherapy

Indolent NHL

- long natural history (patients can live for many years untreated)
- disease of slow cellular accumulation
- Generally incurable with chemotherapy

HL- presentation

Painless Lymphadenopathy often localized to a single LN group (Frequently upper half of the body (Cervical, axillary & Mediastinal LN).

Orderly contagious spread

Waldeyer ring and mesenteric LN rare

Extra nodal uncommon

B symptoms : prognostic

- Weight loss > 10%
- Unexplained pyrexia
- Drenching night sweating

Microscopic features HL

Neoplastic cells : RS cells and its variants

Hodgkin cell

Lacunar cell

Mummified cell

Popcorn cell

Non neoplastic Inflammatory cells

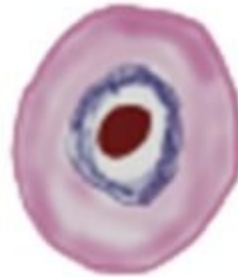
Which form the majority

It can be lymphocytes plasma cells neutrophil
and eosinophil (IL5)

REED STERNBERG CELLS- variants



Classical R S Cell



Mononuclear variant/
Hodgkin cell



Lymphohistiocytic
variant



Multinucleated variant

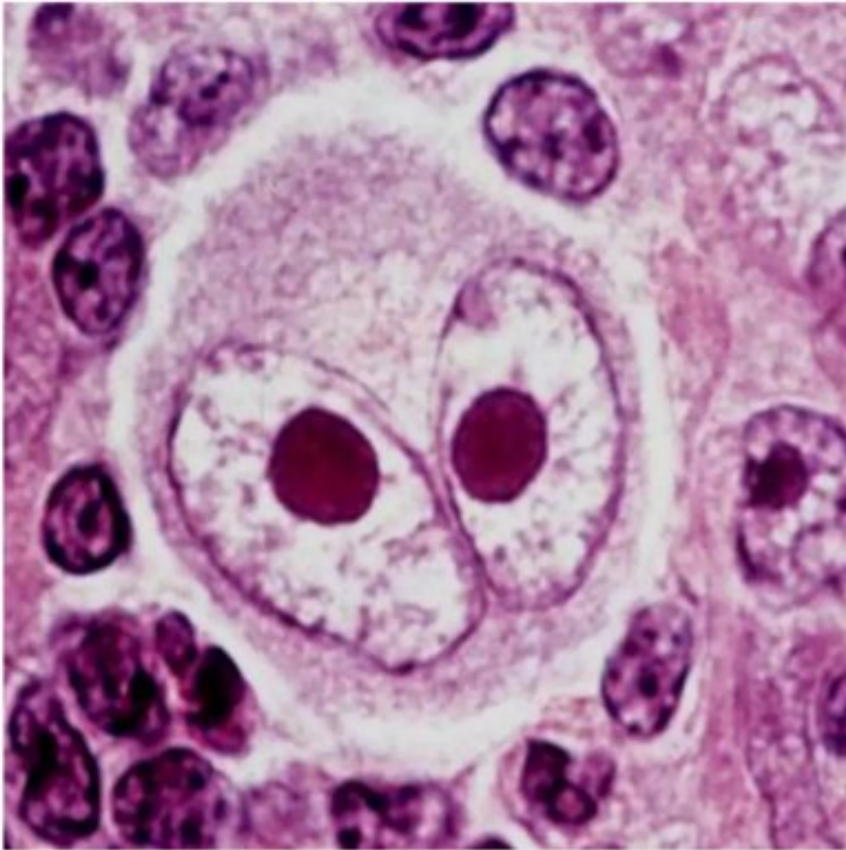


Lacunar cell



Mummified cell

“Reed-Sternberg cell”

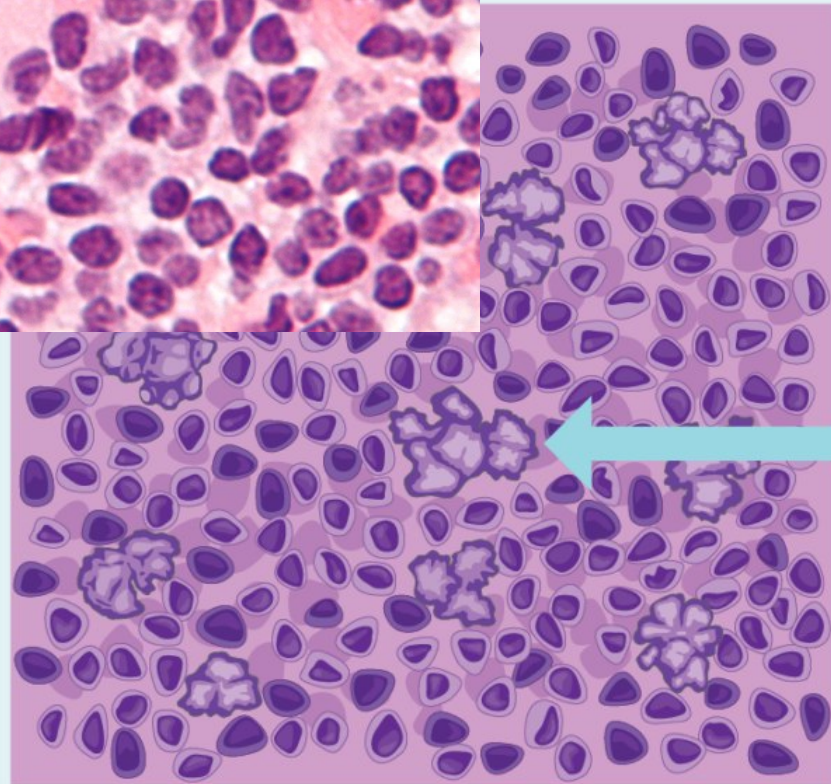


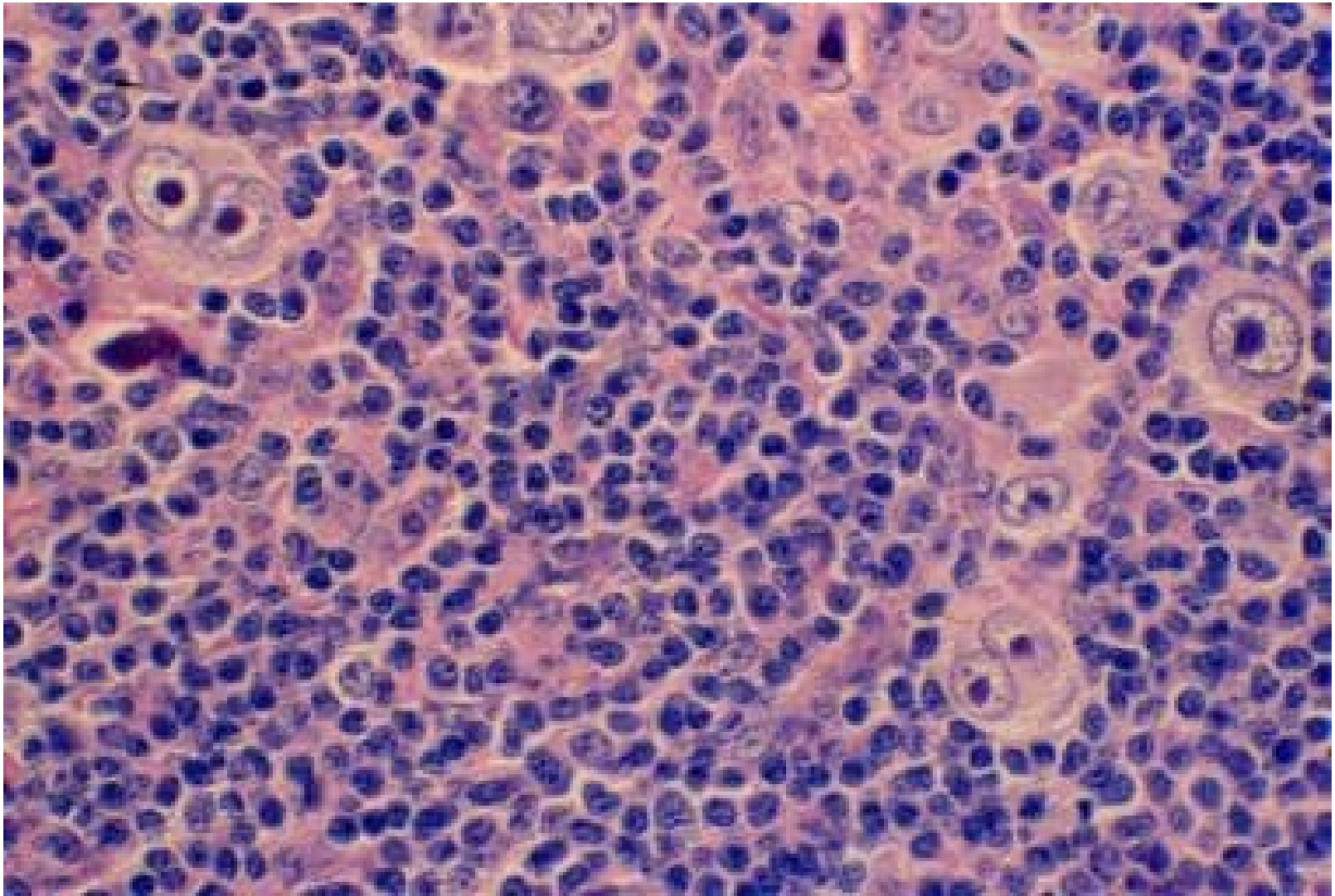
a very large cell with multilobate nucleus or binuclear (two mirror image nuclei) , prominent inclusion-like nucleoli, and abundant slightly eosinophilic cytoplasm.

Popcorn cell

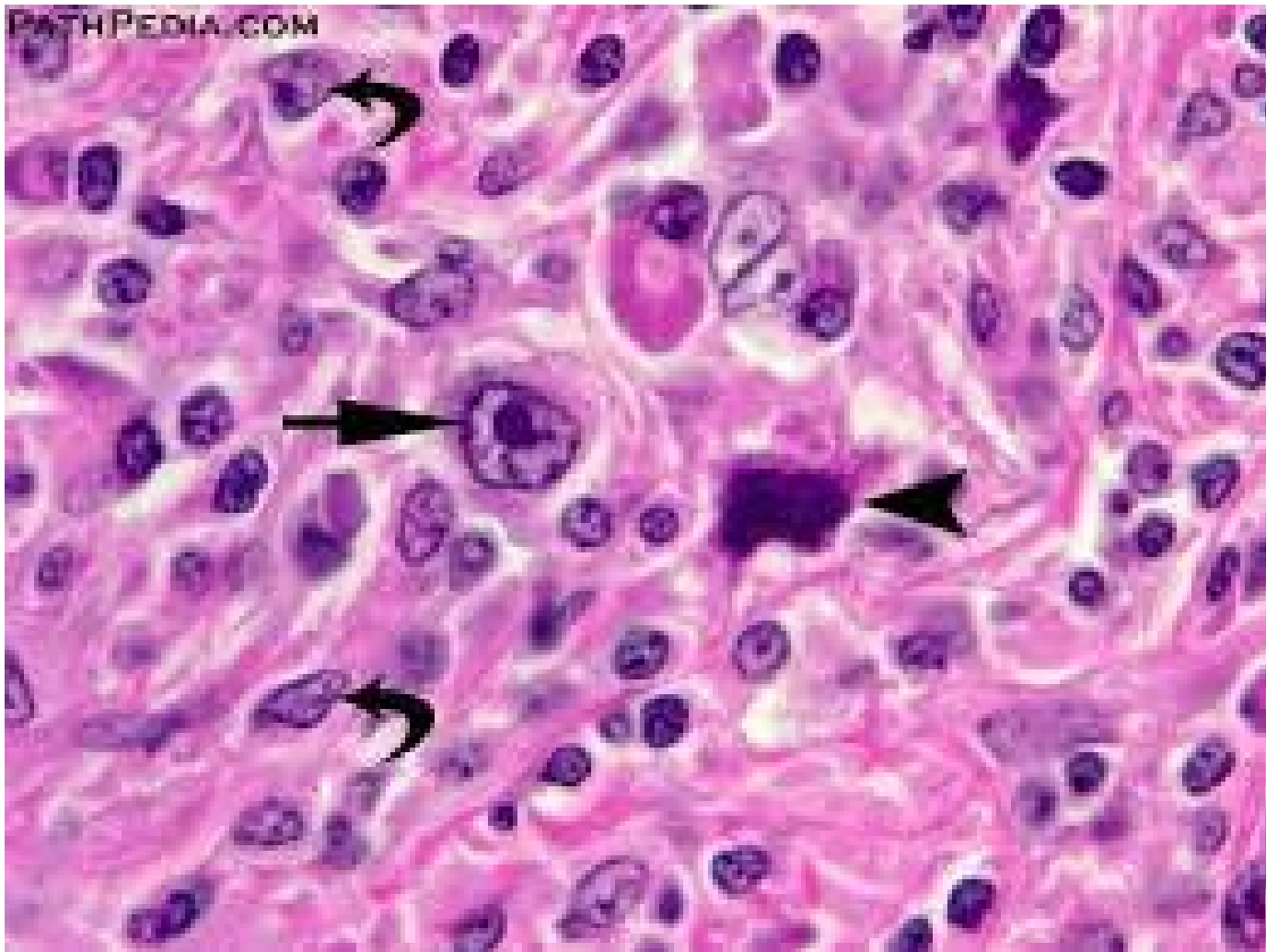


delicate multilobed, puffy
nucleus resembling popped corn

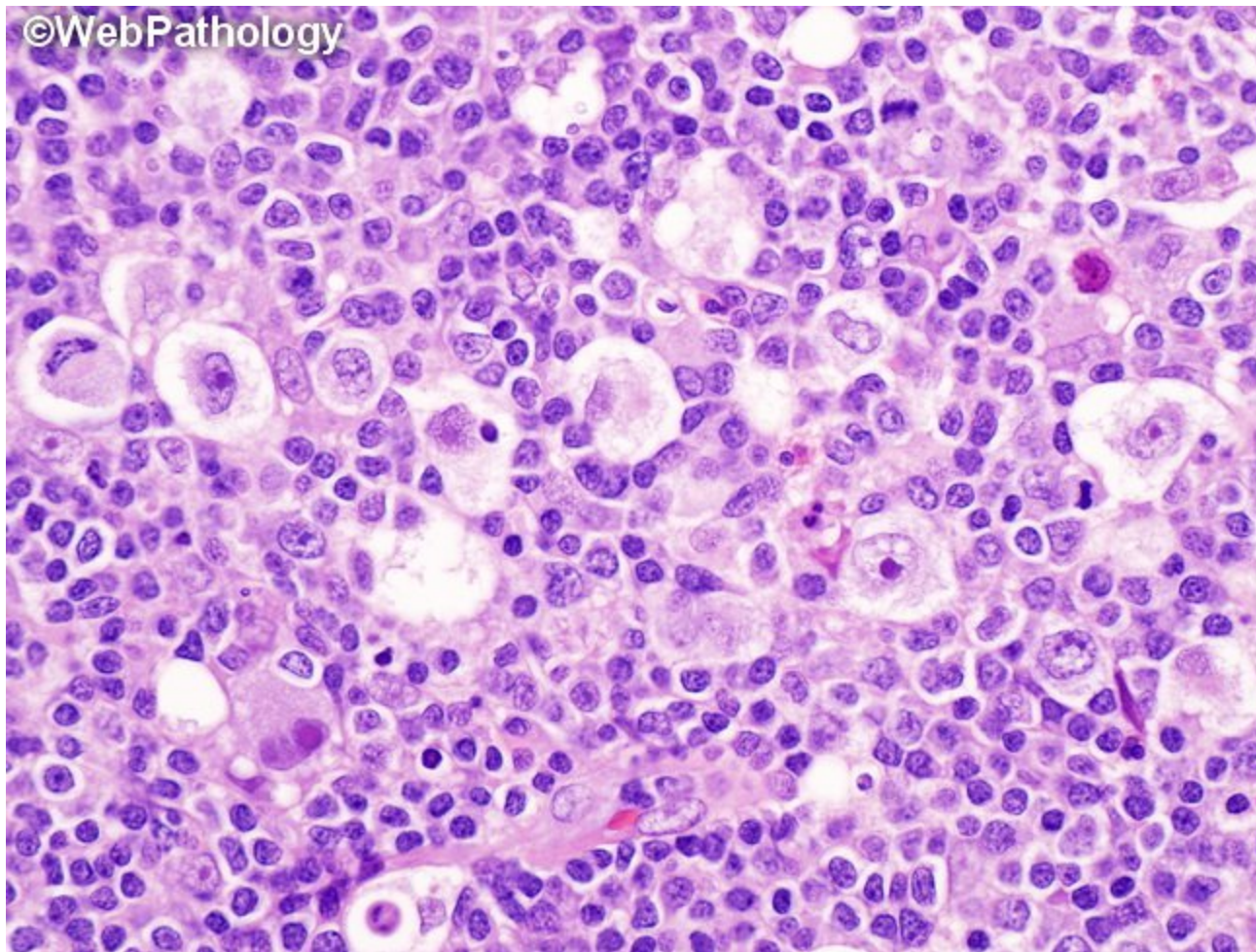




Hodgkin cell : Mononuclear RS variant characterized by a single round or oblong nucleus with large inclusion-like nucleoli



condensed cytoplasm and pyknotic nuclei



Lacunar cells a particular RS cell variant that has a single multilobate nucleus, multiple small nucleoli, and abundant, pale-staining cytoplasm. In sections of formalin-fixed tissue, the cytoplasm often is torn away, leaving the nucleus lying in an empty space (a lacune).

Immunophenotype HL

Classical HL

- Nodular sclerosis
- Mixed cellularity
- Lymphocyte rich
- Lymphocyte depleted

Nodular Lymphocyte predominant HL

Prognosis of HL

The clinical stage is the most important prognostic indicator.

B symptoms also prognostic

The 5-year survival rate of patients with stage I-A or II-A disease is more than 90%.

The 5-year survival rate of patients with stage IV-A or IV-B is around 50%.

Management involve both chemotherapy and radiotherapy

Long-term survivors of radiotherapy protocols are at much higher risk of developing certain malignancies:

lung cancer, melanoma & breast cancer.

Subtypes of Hodgkin Lymphoma

Subtype	Morphology and Immunophenotype	Typical Clinical Features
Nodular sclerosis	Frequent lacunar cells and occasional diagnostic RS cells; background infiltrate composed of T lymphocytes, eosinophils, macrophages, and plasma cells; fibrous bands dividing cellular areas into nodules. RS cells CD15+, CD30+; usually EBV-	Most common subtype; usually stage I or II disease; frequent mediastinal involvement; equal occurrence in males and females (F = M), most patients young adults
Mixed cellularity	Frequent mononuclear and diagnostic RS cells; background infiltrate rich in T lymphocytes, eosinophils, macrophages, plasma cells; RS cells CD15+, CD30+; 70% EBV+	More than 50% present as stage III or IV disease; M greater than F; biphasic incidence, peaking in young adults and again in adults older than 55
Lymphocyte rich	Frequent mononuclear and diagnostic RS cells; background infiltrate rich in T lymphocytes; RS cells CD15+, CD30+; 40% EBV+	Uncommon; M greater than F; tends to be seen in older adults
Lymphocyte depletion	Reticular variant: Frequent diagnostic RS cells and variants and a paucity of background reactive cells; RS cells CD15+, CD30+; most EBV+	Uncommon; more common in older males, HIV-infected individuals, and in developing countries; often presents with advanced disease
Lymphocyte predominance	Frequent L&H (popcorn cell) variants in a background of follicular dendritic cells and reactive B cells; RS cells CD20+, CD15-, CD30-; EBV-	Uncommon; young males with cervical or axillary lymphadenopathy

Nodular sclerosis

Most common type 70%

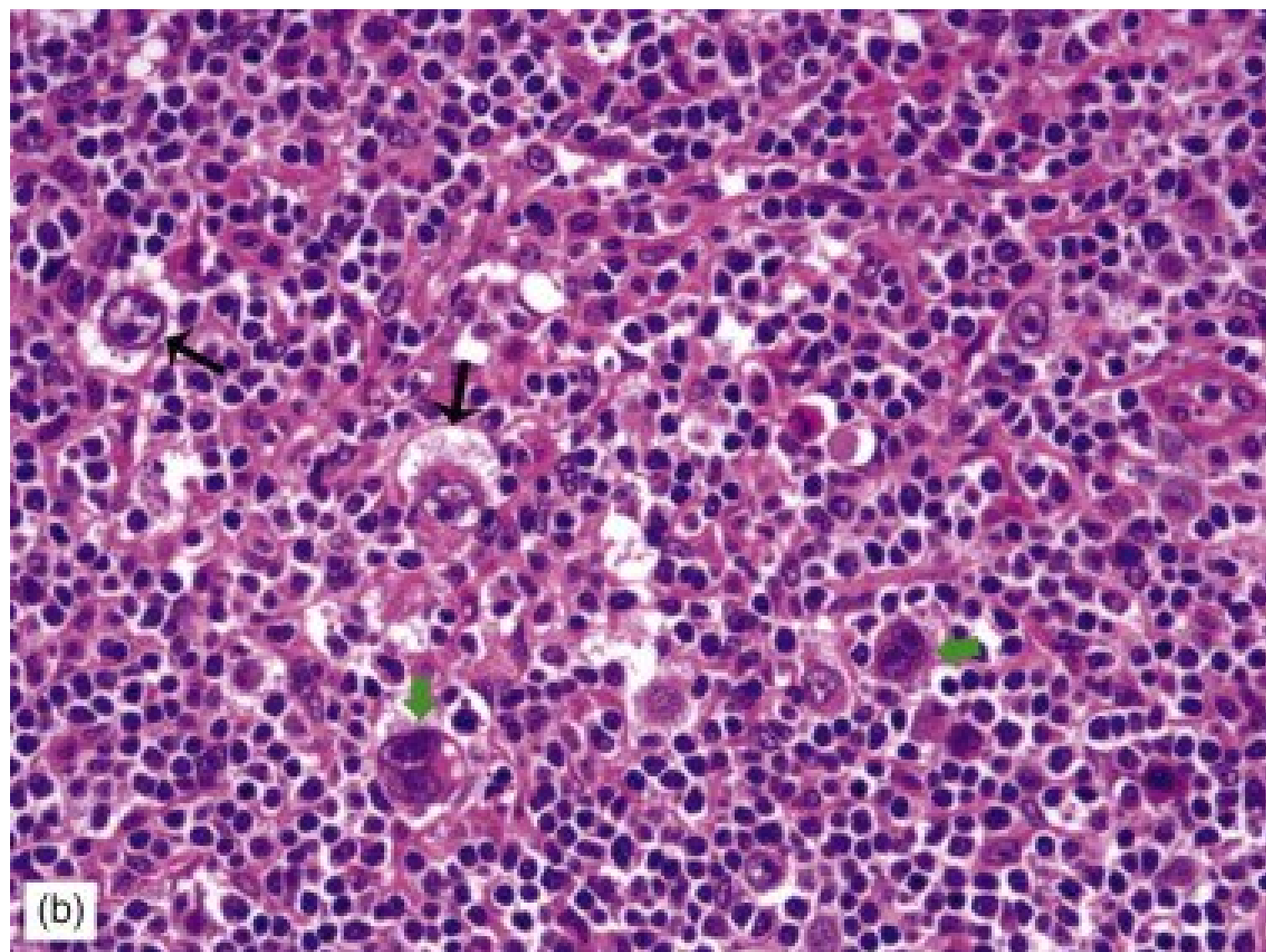
Age : adolescent or young adults , female = male

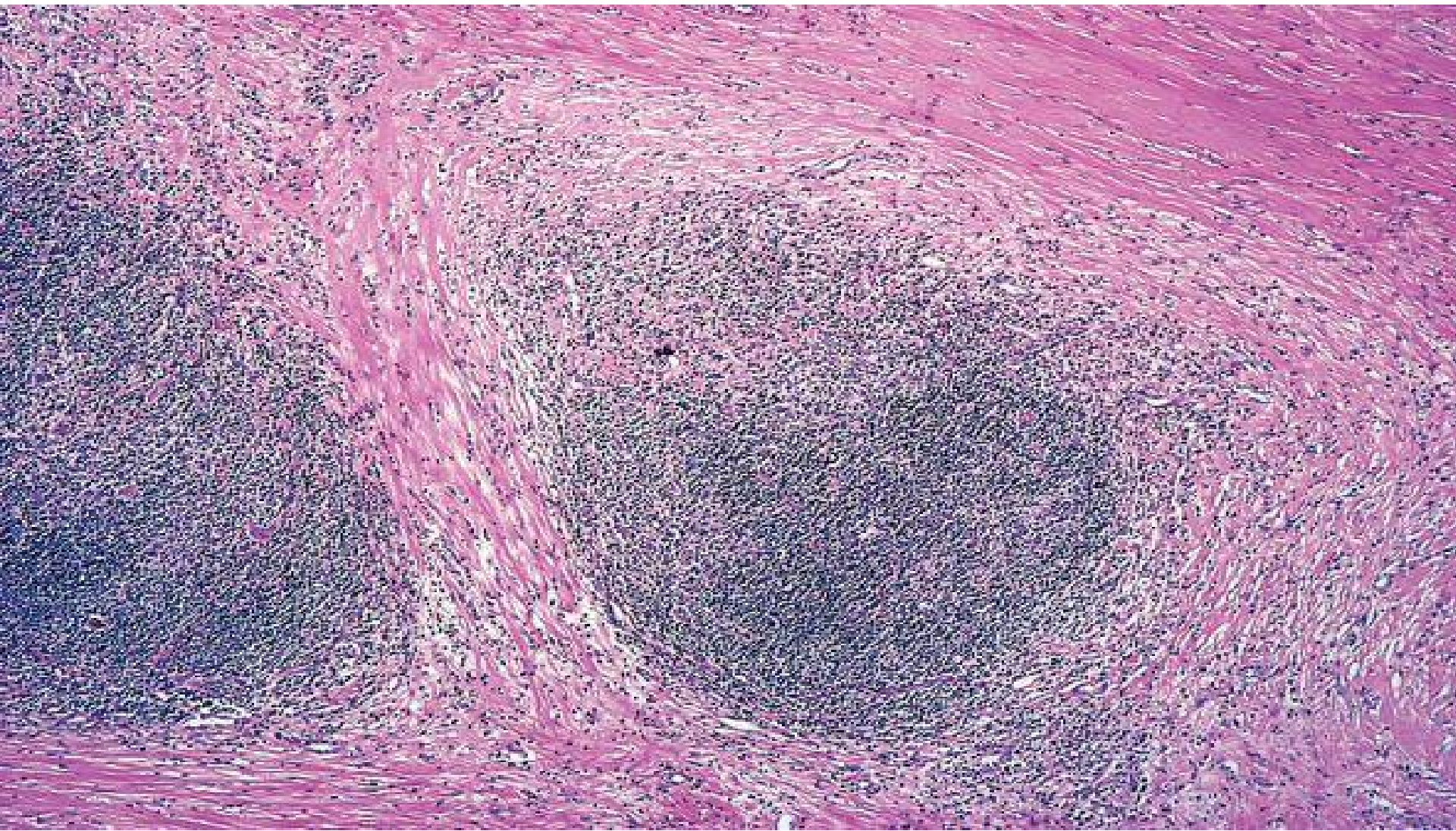
Usually stage 1 or 2 – good prognosis

The normal LN architecture is replaced by cellular nodules which are separated by bands of collagen.

CD15 CD30 +ve CD45-ve EBV usually –ve

Within the cellular nodules is the lacunar cells and few R-S cells .





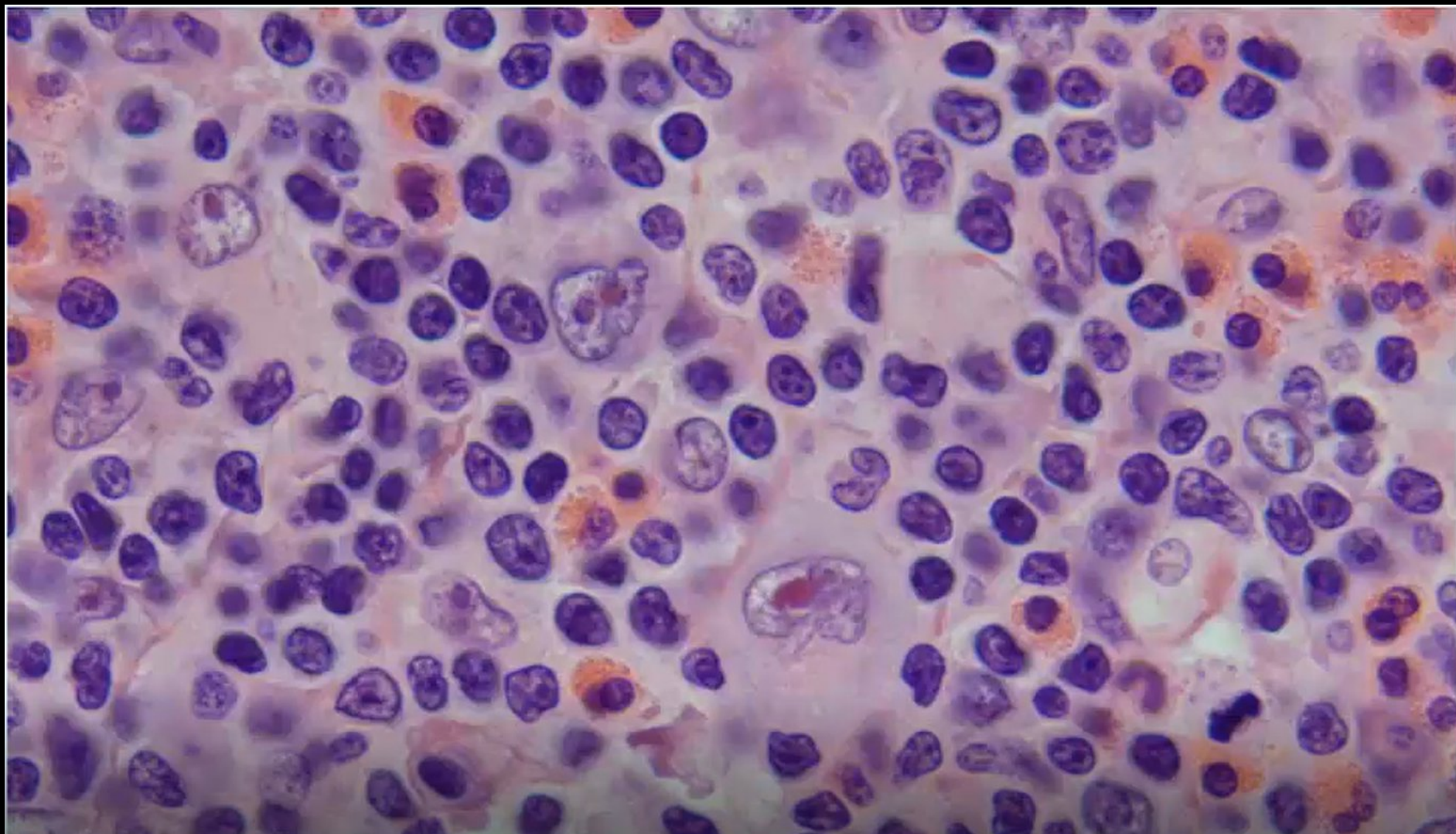
Mixed cellularity

Frequent R-S cells and mononuclear variant in a rich inflammatory background of a mixture of lymphocytes, plasma cells, & eosinophils.

70% EBV +ve

More likely to be disseminated (advanced stages) stage 3 or 4 with B symptoms .

Age mostly above 50 years



Lymphocyte rich HL

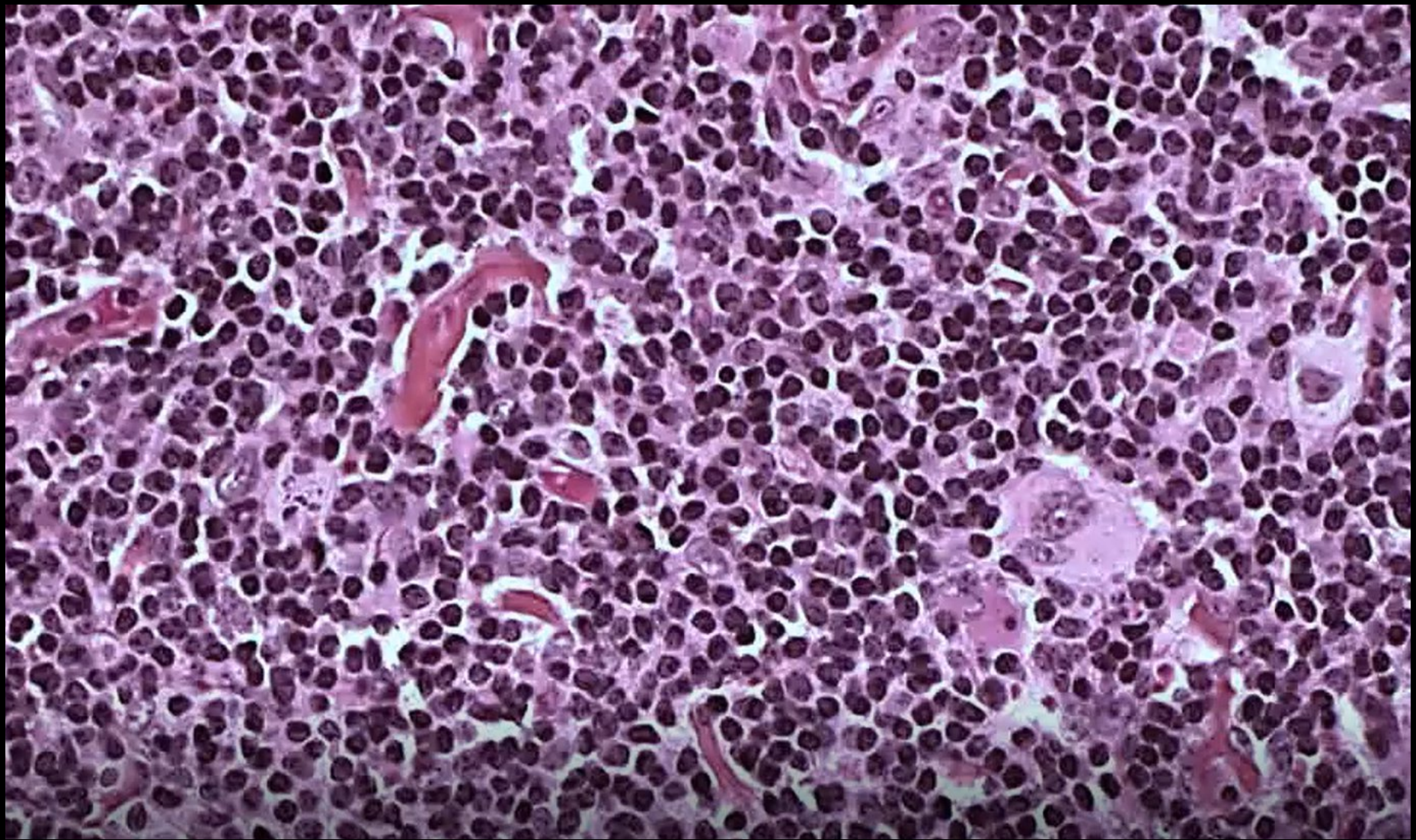
Uncommon

Elderly age group

Lymphocyte-rich has the best prognosis of all types.

Presence of R-S cells in a lymphocyte-rich cellular background

EBV +ve 40%



Lymphocyte depleted HL

Uncommon

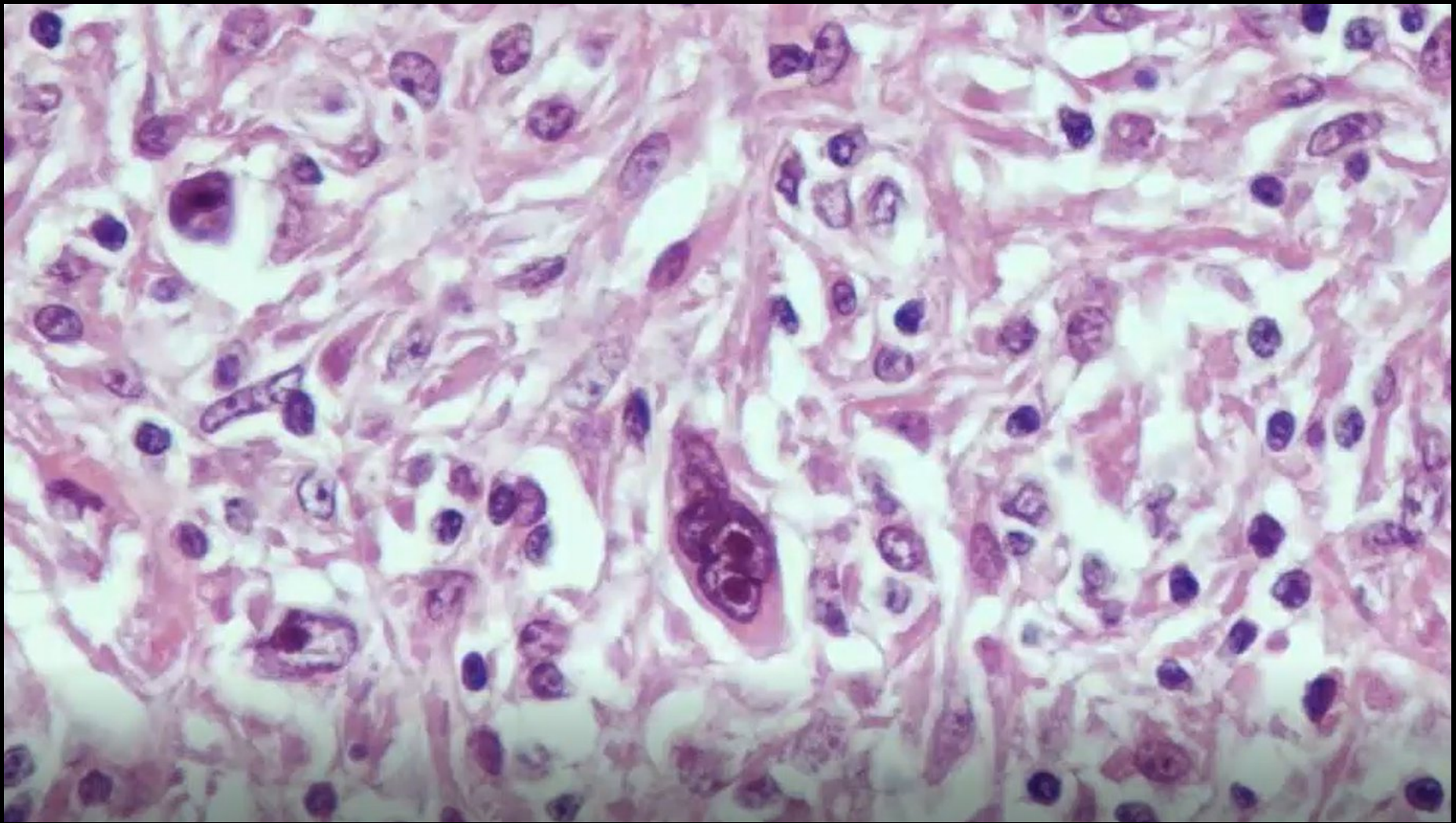
HIV +ve elderly

Advanced stages, Extranodal involvement

The most aggressive type (poor prognosis)

RS cells in paucity of lymphocytes
background

Highly associated with EBV (95%)



Lymphoma

Nodular Lymphocyte predominant HL

Non classical Hodgkin's lymphoma (5% of HL cases)

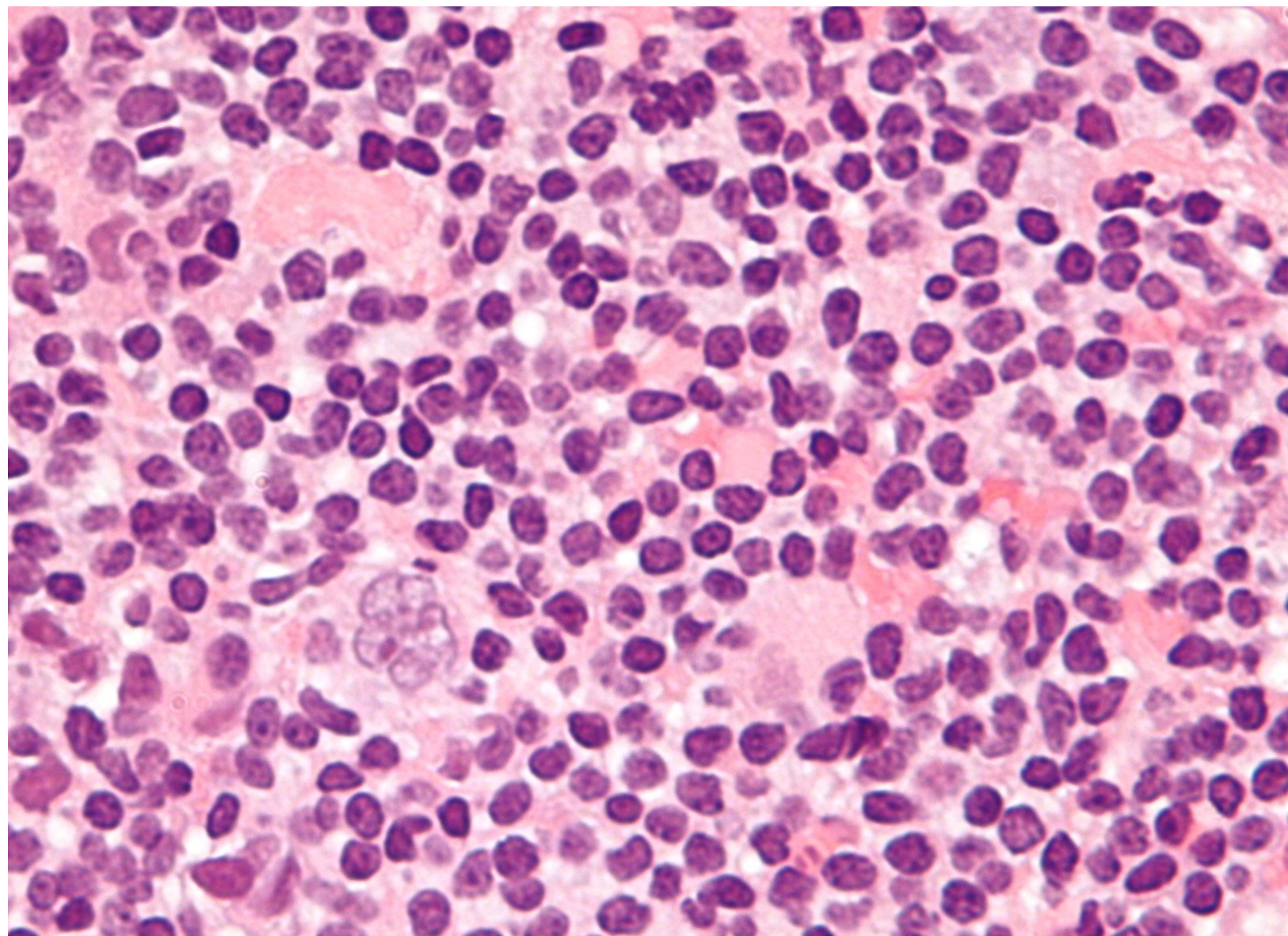
Affects mainly young males

Usually Localized disease cervical and axillary

Characteristic popcorn neoplastic cells

CD45+ve CD15 CD30 –ve EBV –ve

Excellent prognosis



Non Hodgkin Lymphoma

Precursor B/T-cell Lymphoblastic lymphoma/
ALL

Peripheral NH Lymphoma

Low
grade

B-cell NHL

SLL/CLL

Follicular lymphoma

High
grade

Mantle cell lymphoma

Marginal zone lymphoma

DLBL

Burkitt Lymphoma

T-Cell NHL

Mycosis fungoides/Sézary syndrome

Peripheral T cell lymphoma

Precursor lymphoid neoplasms

Two types of diseases:

1. Lymphoblastic lymphoma
2. Lymphoblastic leukemia ALL

They may be of T-cell or B-cell lineage and express the nuclear antigen TdT.

Differentiation depends on the degree of BM involvement:

Heavily involved BM = ALL

Negative BM or mildly involved = Lymphoblastic lymphoma

B cell neoplasms

T cell neoplasms

BONE MARROW

THYMUS



Precursor T
lymphoblastic
lymphoma/
leukemias

Precursor B
lymphoblastic
lymphoma/
leukemias

Small lymphocytic
lymphoma

Chronic
lymphocytic
leukemia

Multiple myeloma



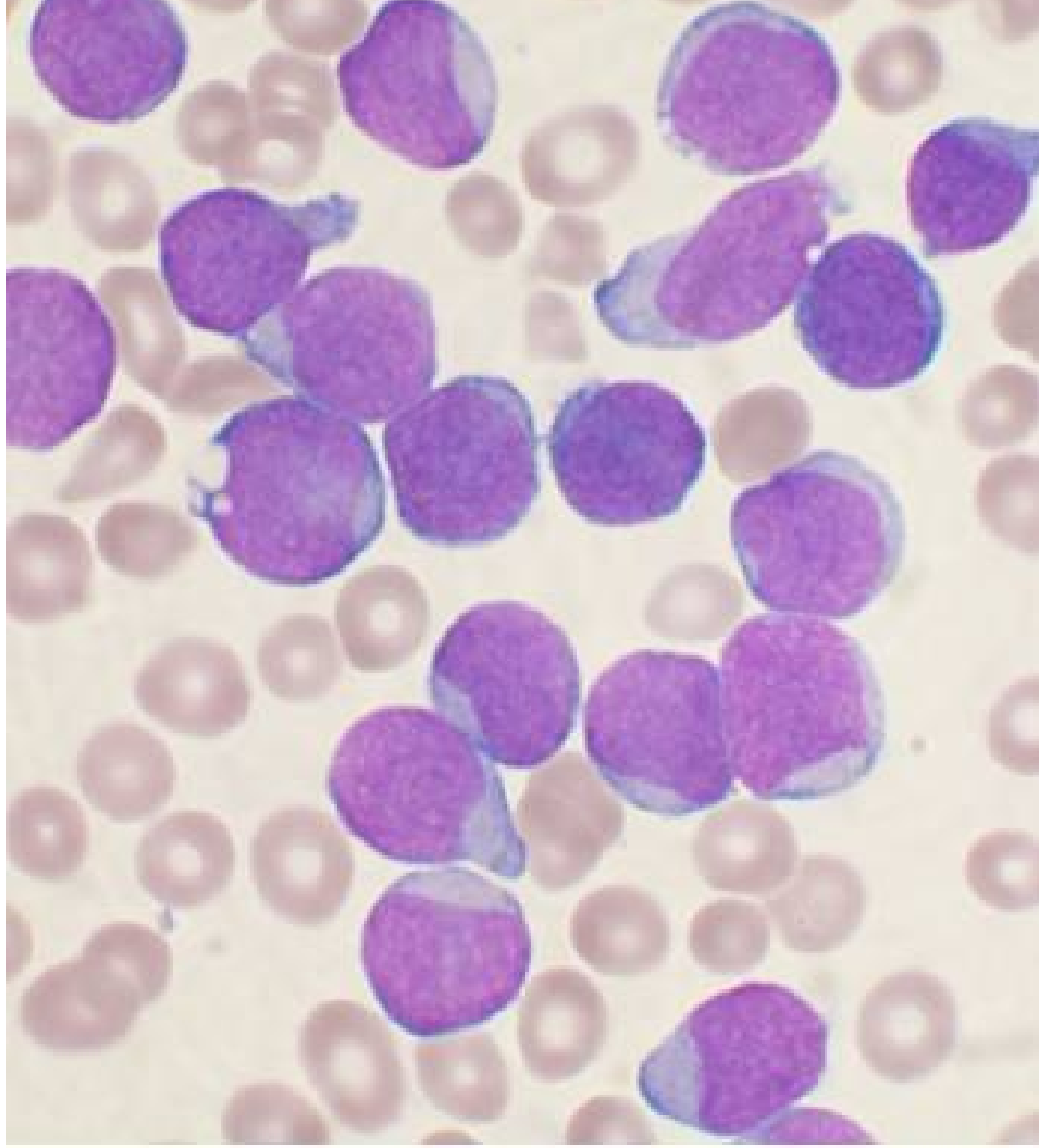
Precursor lymphoid neoplasms

- Are neoplasms composed of immature B or T cells (lymphoblast)
- **B cell lymphoblasts**
 - 85% of all precursor tumors
 - Typically childhood 0-5 yrs (BM pre b cell is greatest in this age)
 - Manifest as leukemia ALL – most common cancer pediatric age
- **T cell lymphoblasts**
 - Manifest as thymic lymphomas in mediastinal region SVC syndrome or compression on trachea
 - Adolescent males (max. thymic size)
 - However overlap is considered as many T cell lymphomas may evolve leukemic pic

Clinical features

- the following:
- **Cytopenias** symptoms related to depression of marrow function, including fatigue from anemia; fever, reflecting infections secondary to neutropenia; and bleeding due to thrombocytopenia
- Mass effects caused by neoplastic infiltration, including **bone pain** resulting from marrow expansion and infiltration of the subperiosteum
- **Central nervous system manifestations** resulting from meningeal spread, such as headache, vomiting, and nerve palsies
- **Lymphadenopathies hepatosplenomegally**
- + compression from mediastinal mass

- Morphology :both B- and T-ALL, the tumor cells have scant basophilic cytoplasm and nuclei with delicate, finely stippled chromatin and small nucleoli
- Immunophenotype : TdT +ve CD3 CD 19



- Despite its highly malignant natural history, pediatric
- ALL is one of the great success stories of oncology. With aggressive chemotherapy, about 95% of children with ALL obtain a remission, and 75% to 85% are cured. only 35% to 40% of affected adults are cured

Small lymphocytic lymphoma
(SLL)
Chronic lymphoblastic leukemia
CLL

Chronic lymphocytic leukemia (CLL) and small lymphocytic lymphoma (SLL) are essentially identical, differing only in the extent of peripheral blood involvement.

Chronic lymphocytic leukemia (CLL): neoplasm of mature B cells with characteristic immunophenotype showing peripheral lymphocytosis ($\geq 5 \times 10^9/L$) with or without nodal or extranodal manifestation

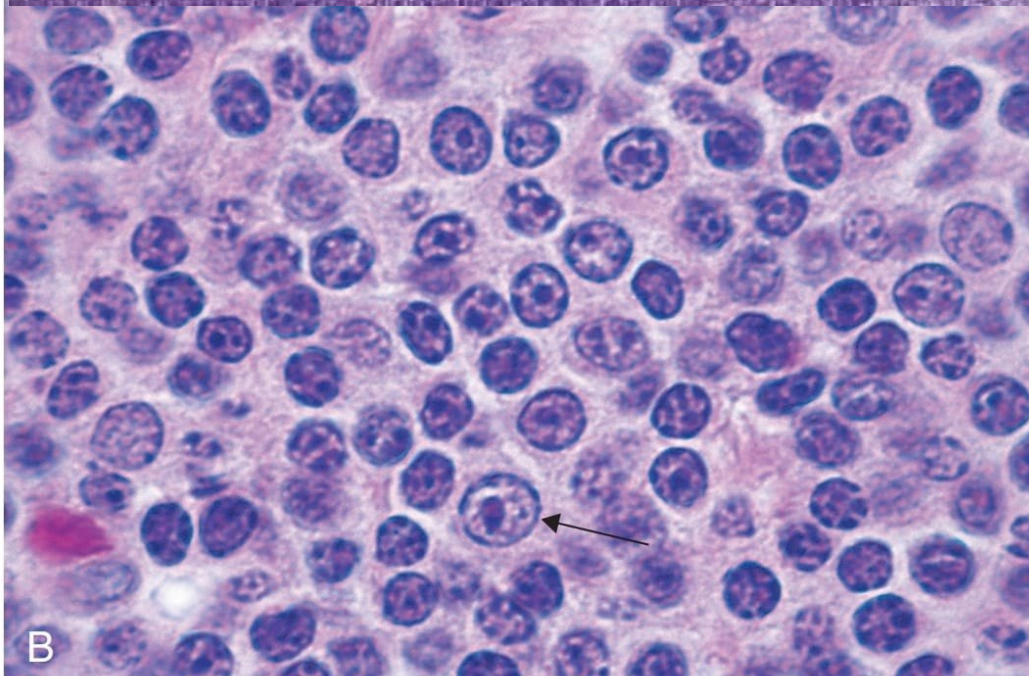
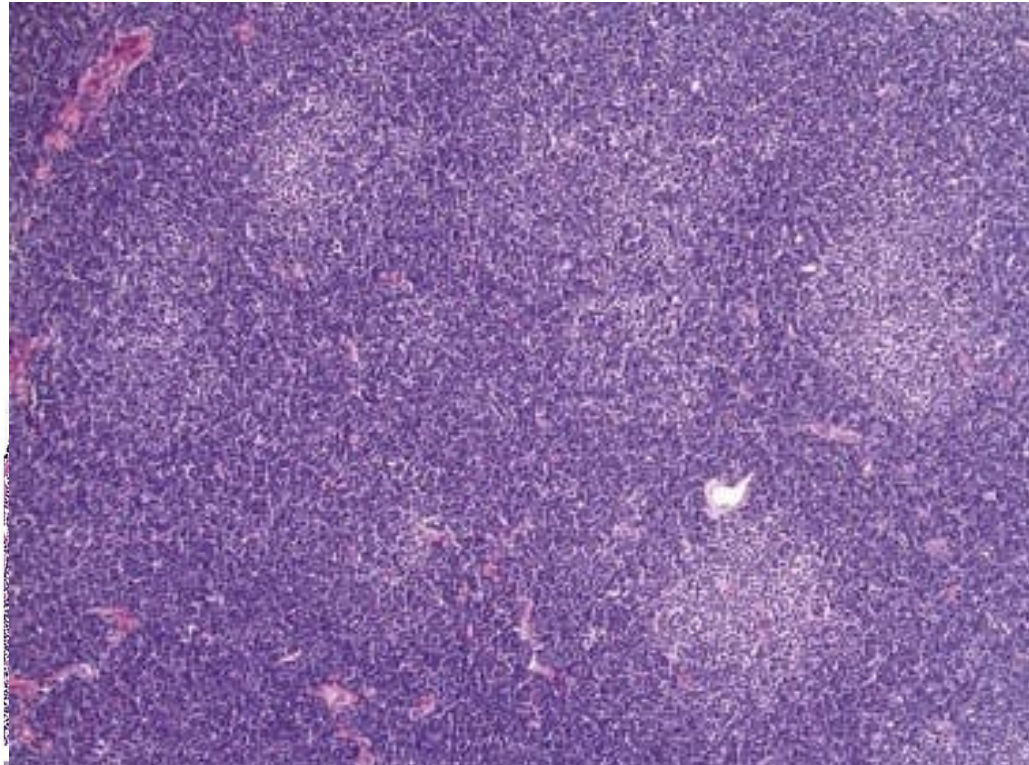
Small lymphocytic lymphoma (SLL): $< 5 \times 10^9/L$ CLL-like cells in peripheral blood with nodal or extranodal manifestation, usually with bone marrow involvement

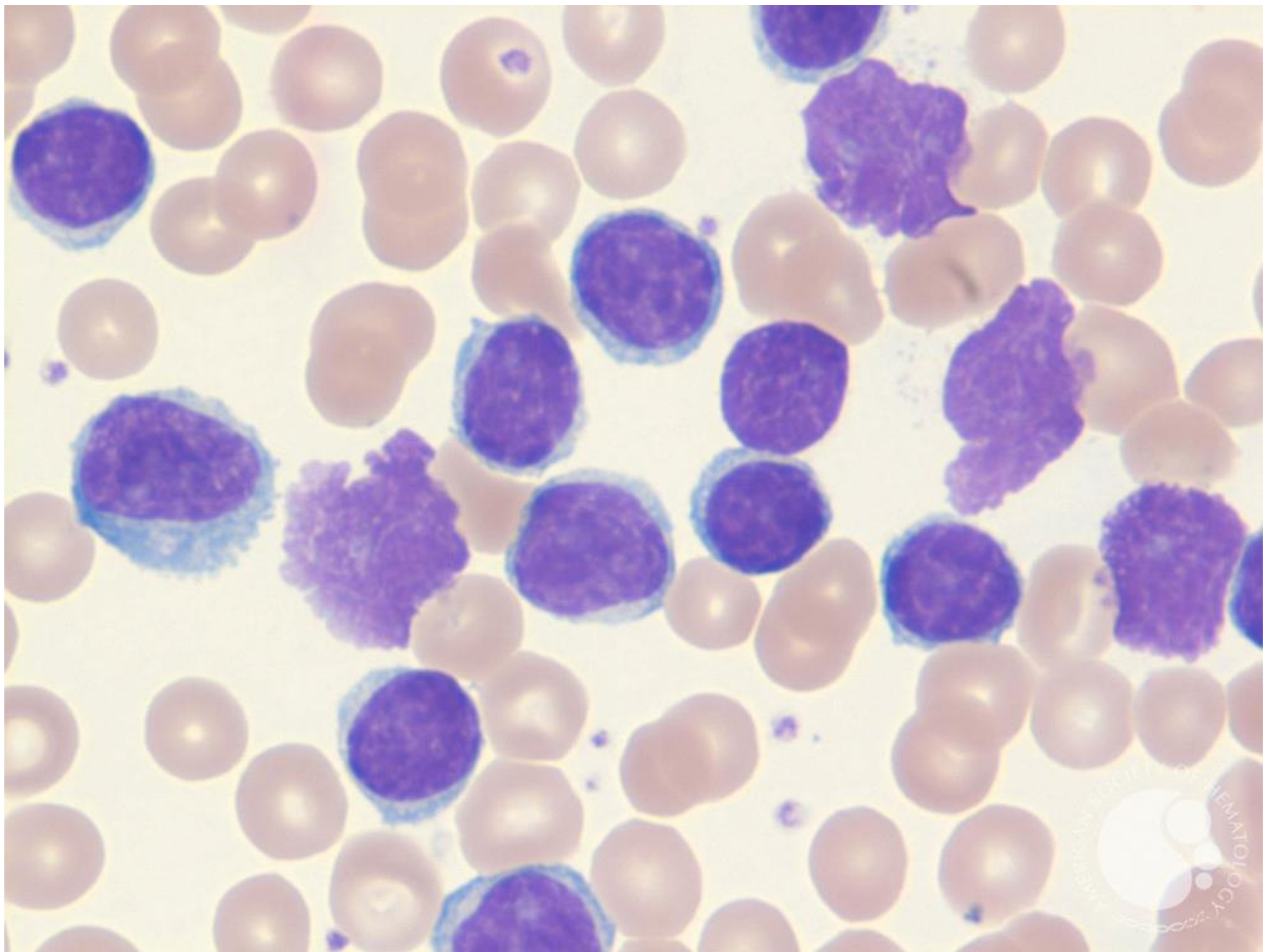
CLL most common adult type leukemia (1/3 of all leukemia)

- Clinical features
- Frequently no symptoms
- Lymphadenopathy, splenomegaly are common
- Anemia, thrombocytopenia and neutropenia related symptoms frequently – Autoimmune dz
- suppresses normal B cell function, often resulting in hypogammaglobulinem so increased susceptibility infections
- A small fraction of tumors transform to aggressive tumors resembling diffuse large B cell lymphoma (Richter transformation); after transformation occurs, the median survival is less than 1 year

- Immunophenotype :
- B cell markers CD19 CD20
- CD5 CD23
(CD5 +ve in CLL/SLL and mantle zone lymphoma while CD23+ve in CLL/SLL and –ve in Mantle lymphoma)
- Molecular :
karyotypic abnormalities, the most common of which are trisomy 12 and deletions involving portions of chromosomes 11, 13, and 17.

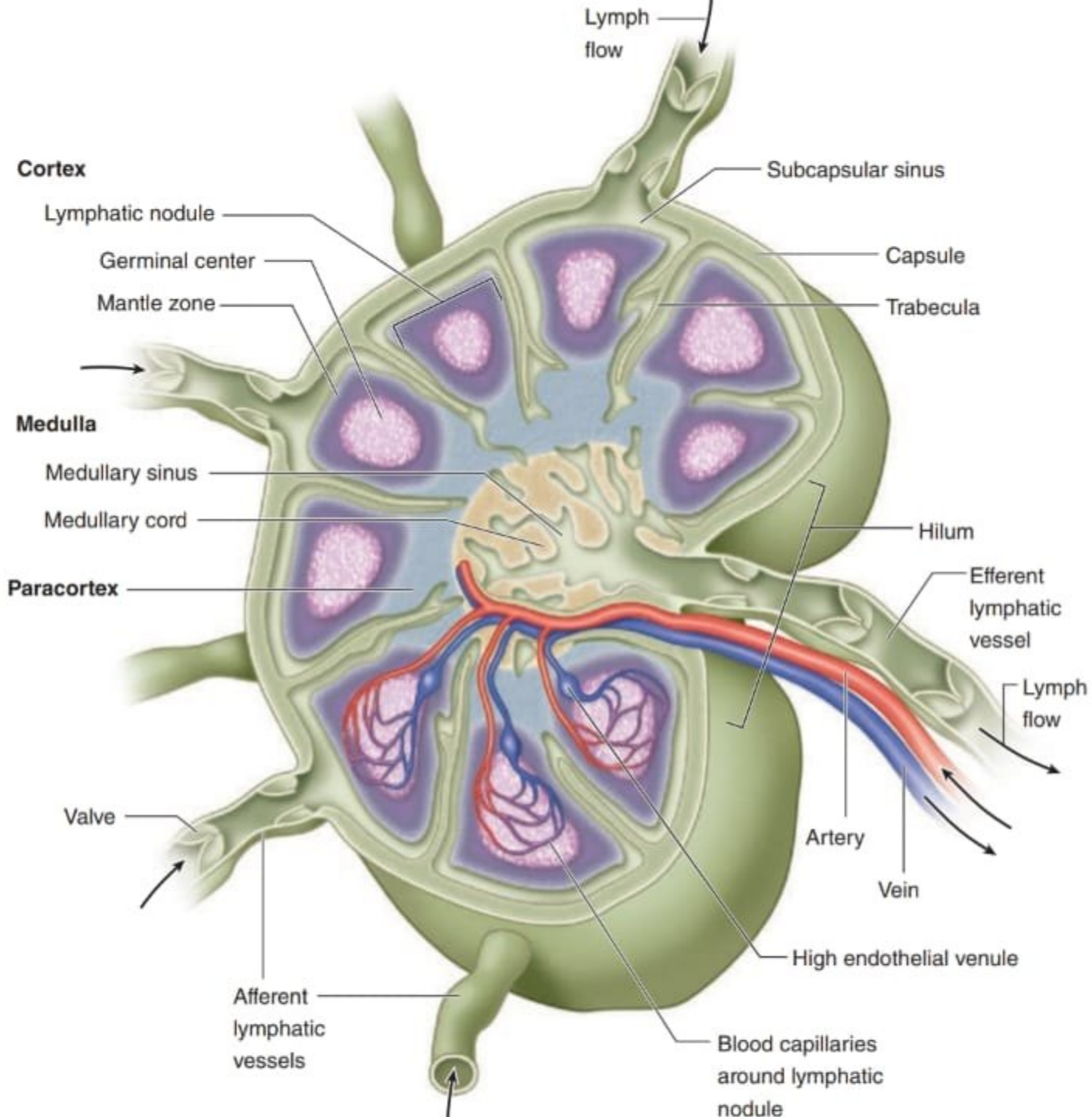
- Morphology :
- Lymph nodes :
- Diffuse effacement of parenchyma by small, dark
Round nucleus, small nucleoli and scant cytoplasm
- Ill defined, pale proliferation centers (pseudofollicles)
which are pathognomonic for CLL/SLL, composed of
prolymphocytes-larger cells with central large nucleoli
- Peripheral blood film :
- lymphocytosis featuring small, mature-looking
lymphocytes.
- These circulating cells are fragile and during the
preparation of smears many are disrupted, producing
characteristic smudge cells.

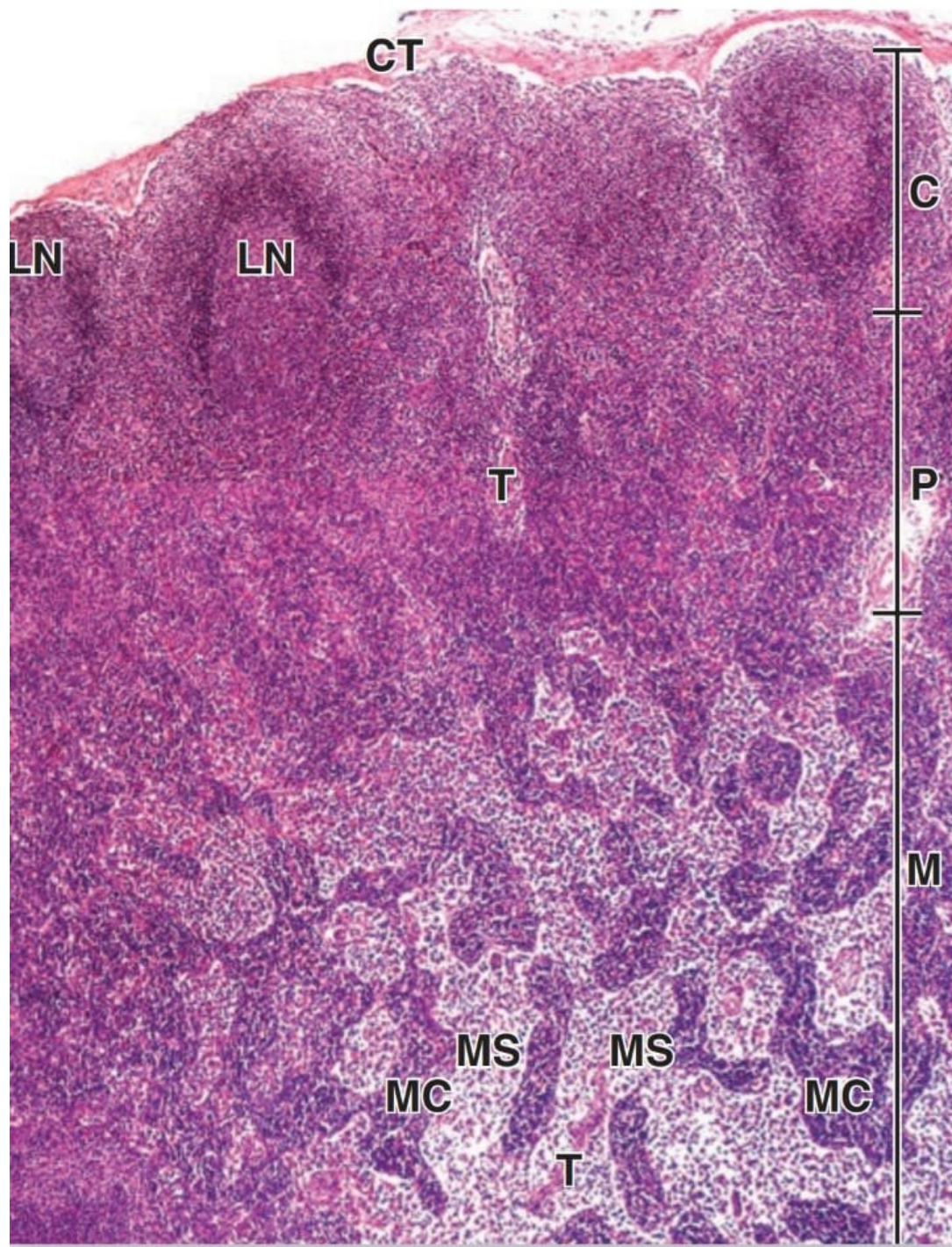




The course and prognosis of CLL/SLL are highly variable and depend on the disease stage and genetic findings.

Management : immunochemotherapy
however, cure may only be achieved with HSCT hematopoietic stem cell transplantation, which is reserved for relatively young patients who fail conventional therapies.





FOLLICULAR LYMPHOMA

40% of the adult NHLs . Most common indolent NHL

Clinical features :

Indolent dz

Commonly wide nodal spread

Usually disseminated at diagnosis 80% BM affection (cytopneias and recurrent infections)

A subset progress rapidly and transform to an aggressive DLBCL

Molecular :

t(14;18) (IgH ; BCL2)

BCL2 antiapoptotic gene

Immunophenotype :

CD 20

CD 10

BCL 2

- Morphology :

Nodular proliferation

Predominant neoplastic cells are centrocytes

Mixed with centroblasts

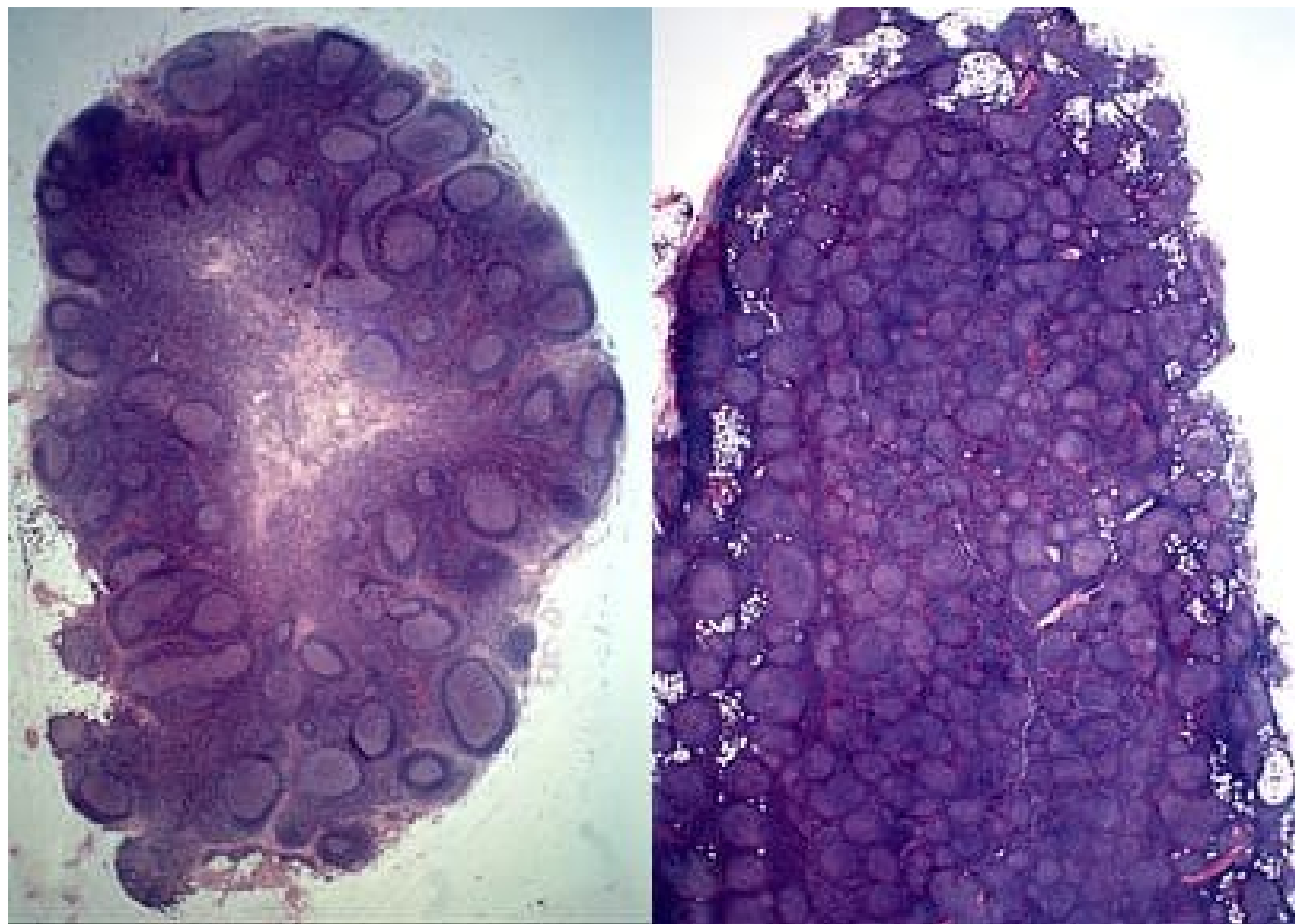
If centroblast predominate this correlate with more aggressive clinical behavior

Follicular lymphoma vs reactive follicular hyperplasia

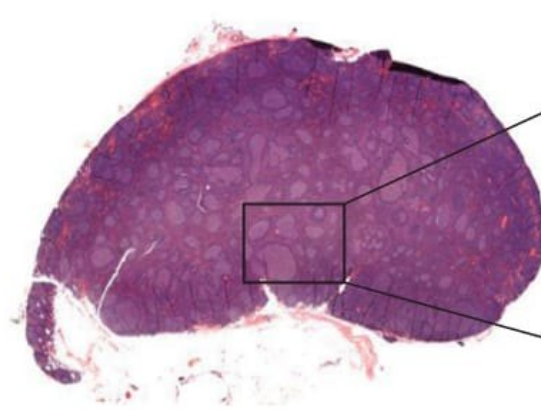


Centrocyte like: smaller lymphoid cells, with cleaved nuclear contour & scant cytoplasm.

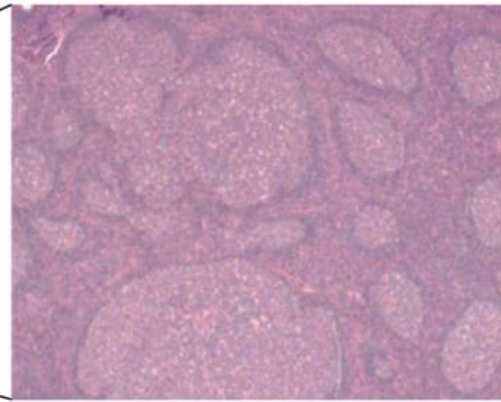
Centroblast like: larger lymphoid cells with several nucleoli & mod



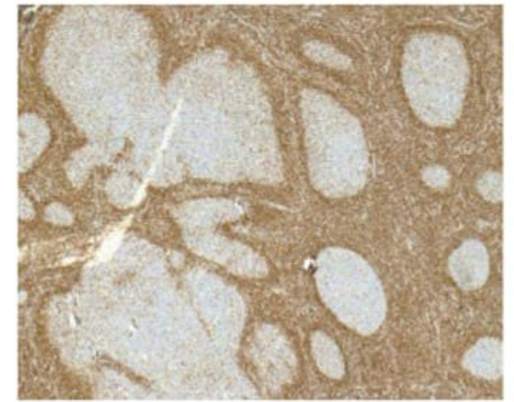
(a)



H&E x4

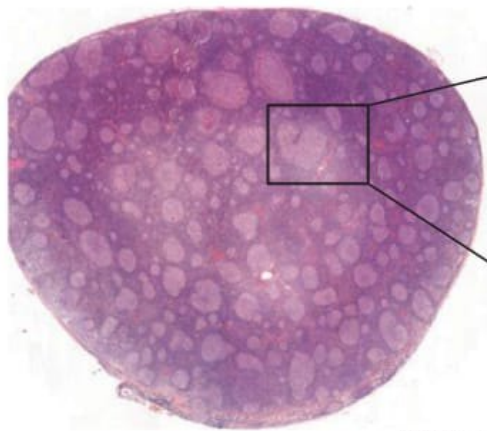


H&E x20

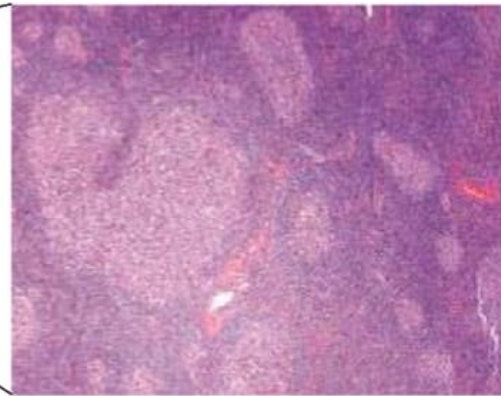


Anti-Bcl2 x20

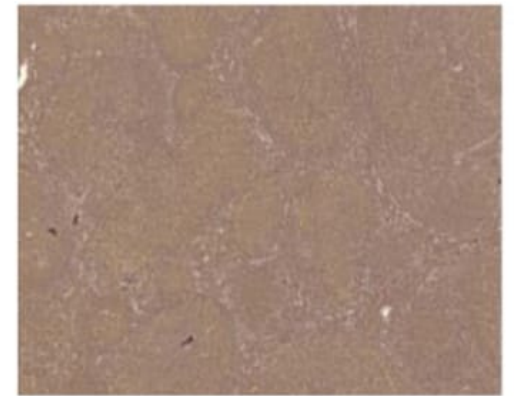
(b)



H&E x4



H&E x20



Anti-Bcl2 x20

Mantle cell lymphoma

- Mantle cell lymphoma is composed of cells resembling the naive B cells found in the mantle zones of normal lymphoid follicles .

- Clinical Features.

Most patients present with fatigue and generalised lymphadenopathy and usually disseminated to extranodal the bone marrow, spleen, liver, and (often) the gastrointestinal tract.

(lymphomatoid polyposis).

These tumors are moderately aggressive and incurable

usually diagnosed stage 4.

The median survival is 4 to 6 years.

- Molecular

t(11;14) (cyclin D1 ; IgH)

Cyclin D1 Promotes G1 to S phase progression during cell cycle

Immunophenotype

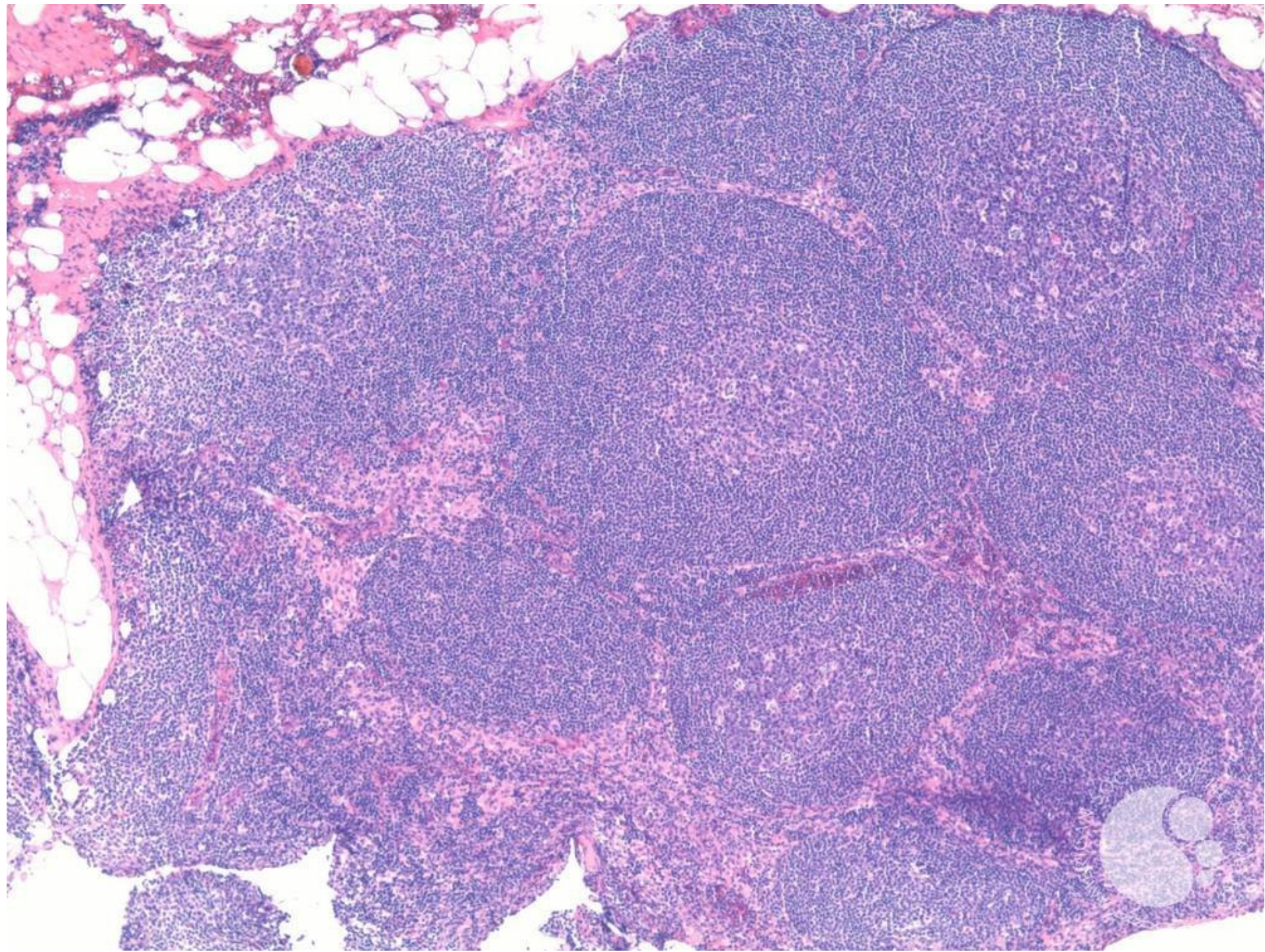
CD 20 CD5 Cyclin D1

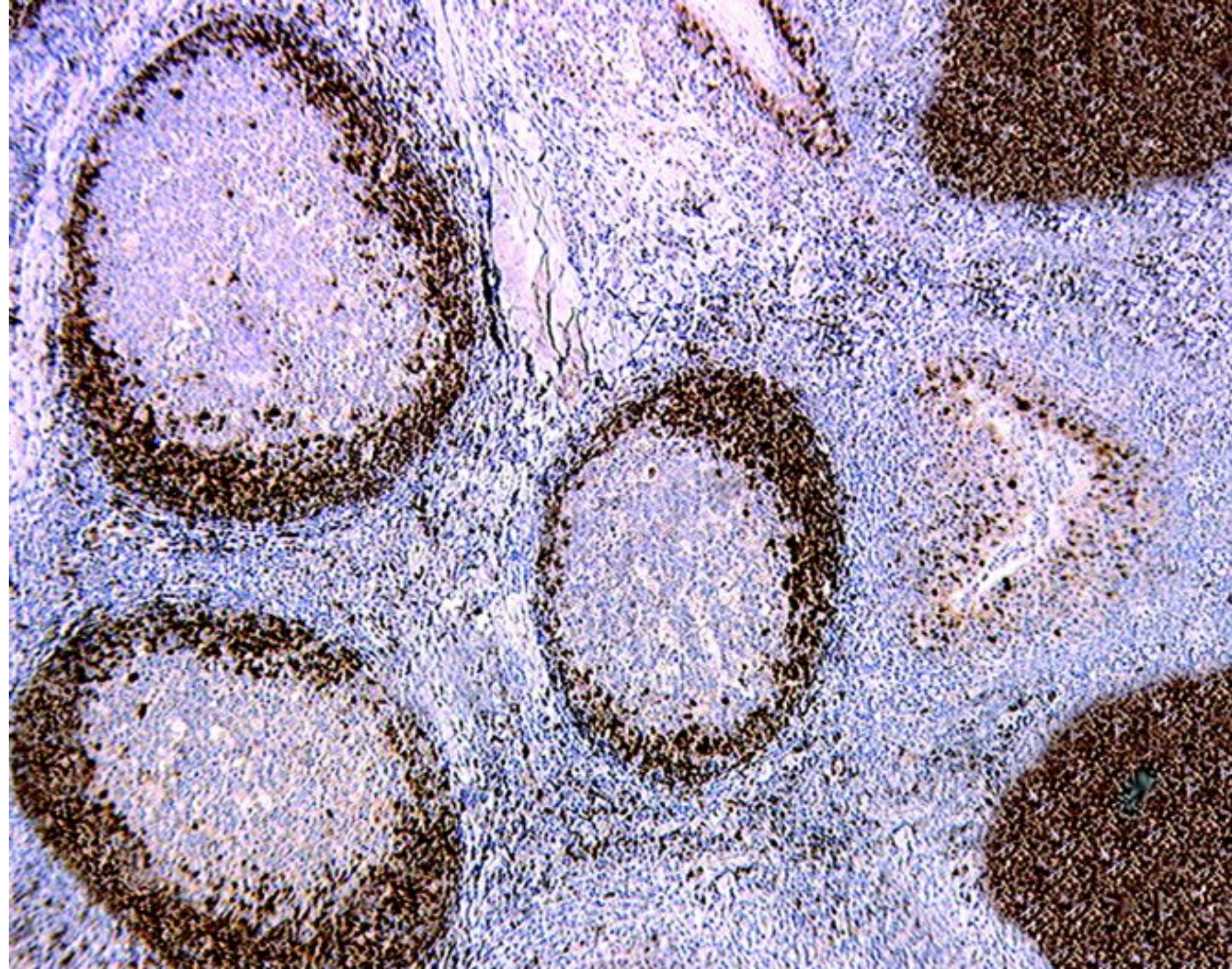
Morphology

Diffuse > nodular > mantle zone growth patterns

In diffuse pattern No proliferative centers (VS CLL)

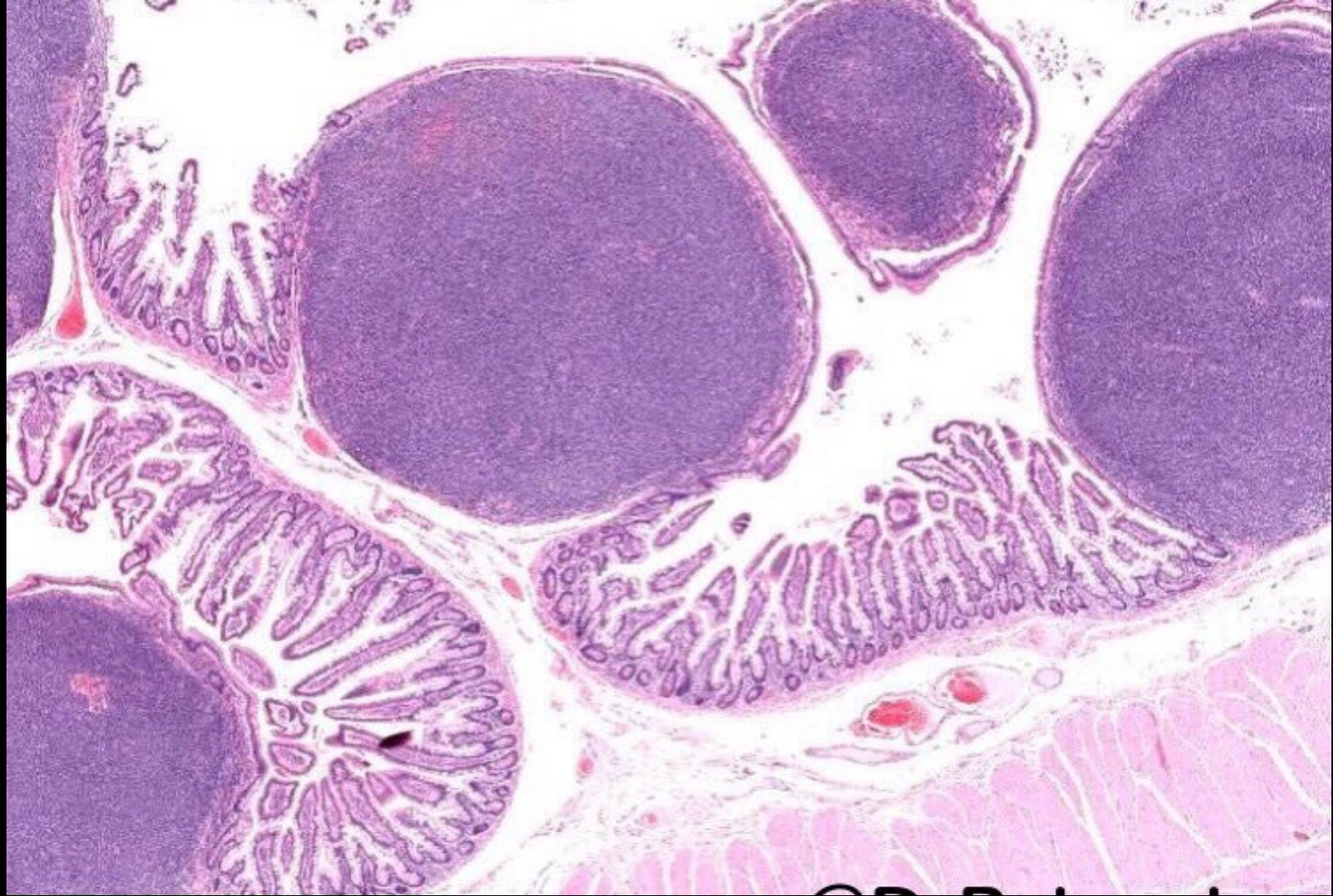
Small to medium monomorphic lymphoid neoplasm - irregular border clumped chromatin nucleolus unclear





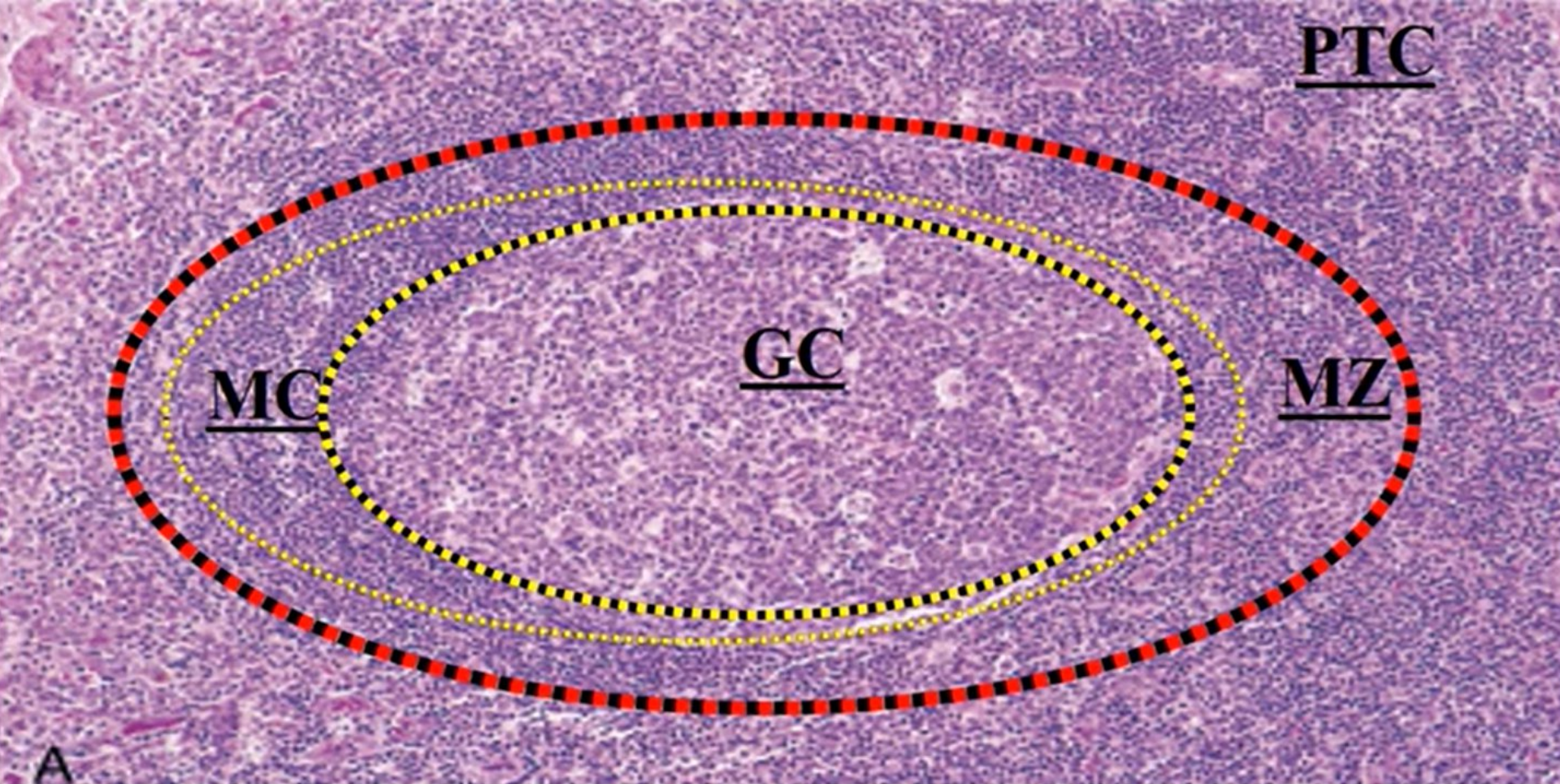
May.
11:5

3F
+ 1/20
AUTO +5



FR:F/I
MM:FICE
RC:REC
(3.8) 12.8
12.8

Frequent GIT involvement by submucosal polyps
(lymphomatoid polyposis)



Origin of some lymphoid neoplasms

GC (Germinal center cells): DLBCL, Fol.L, Burk. L, HL

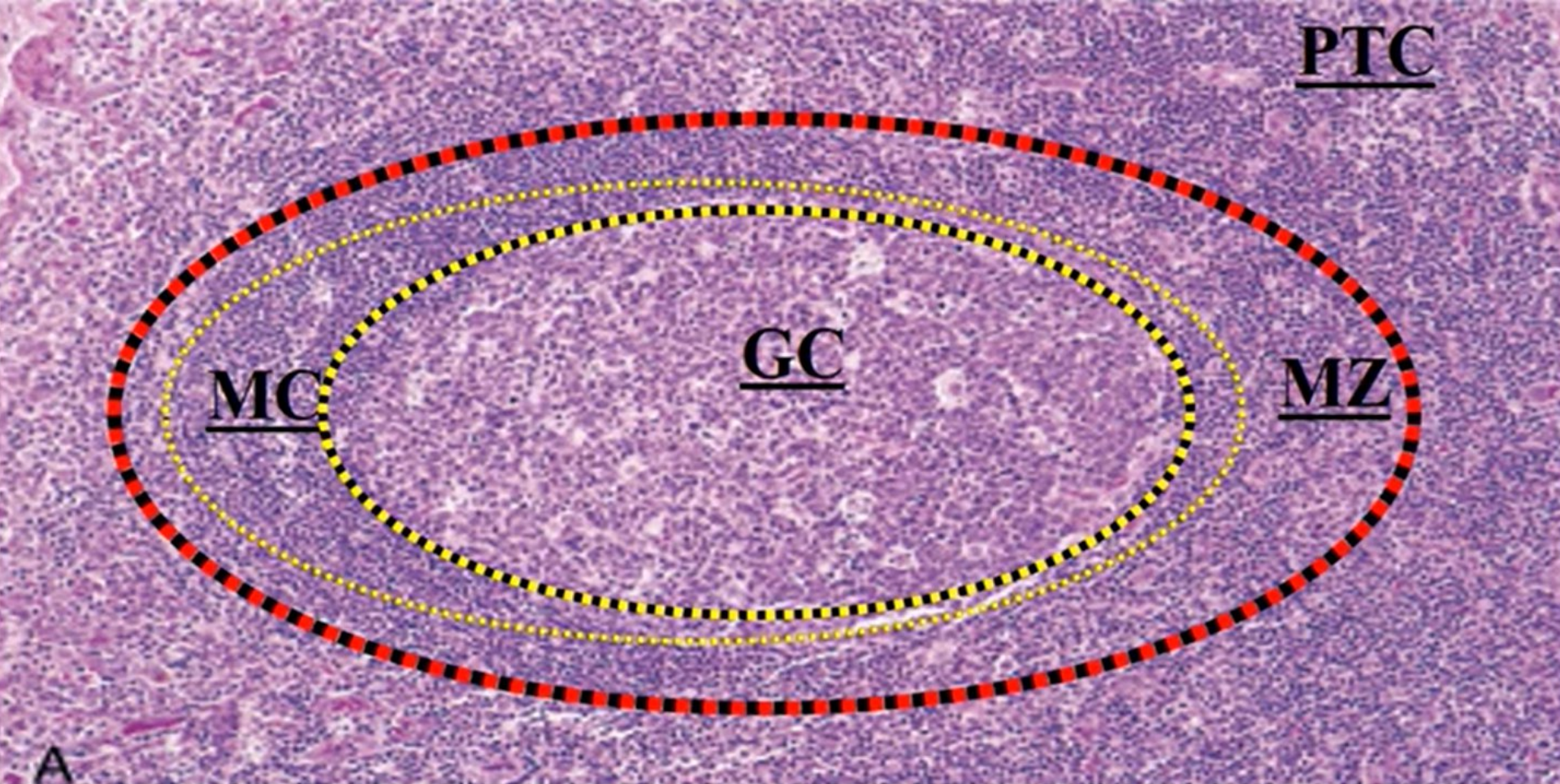
MC (mantle cell zone): Mantle Cell L.

MZ (marginal Zone): Marginal Zone L, SLL/CLL.

PTC (peripheral T-cell zone) : T-cell L.

Marginal zone lymphoma

- Typically extranodal
- gastric MALT -most common site- spleen salivary gland
- Results from chronic inflammatory process
Chronic antigenic stimulation(H. pylori in gastric mucosa)
Chronic autoimmune disease (sjogren salivary glands – Hashimoto thyroiditis)
- Management
- irradiation cause
- if localized surgical excision followed by radiotherapy



Origin of some lymphoid neoplasms

GC (Germinal center cells): DLBCL, Fol.L, Burk. L, HL

MC (mantle cell zone): Mantle Cell L.

MZ (marginal Zone): Marginal Zone L, SLL/CLL.

PTC (peripheral T-cell zone) : T-cell L.

DLBL (diffuse large B-cell lymphoma)

Most common type NHL 45% - older patients .

Rapidly enlarging LN mass.

Extranodal (GIT, skin, bone, CNS, BM, Liver, spleen)

Molecular

30%>> t(14,18) BCL2 over expression

30% BCL6 activating point mutation – transcription regulating in germinal center

IPT: CD19,CD20,BCL2 , C-MYC , double hit

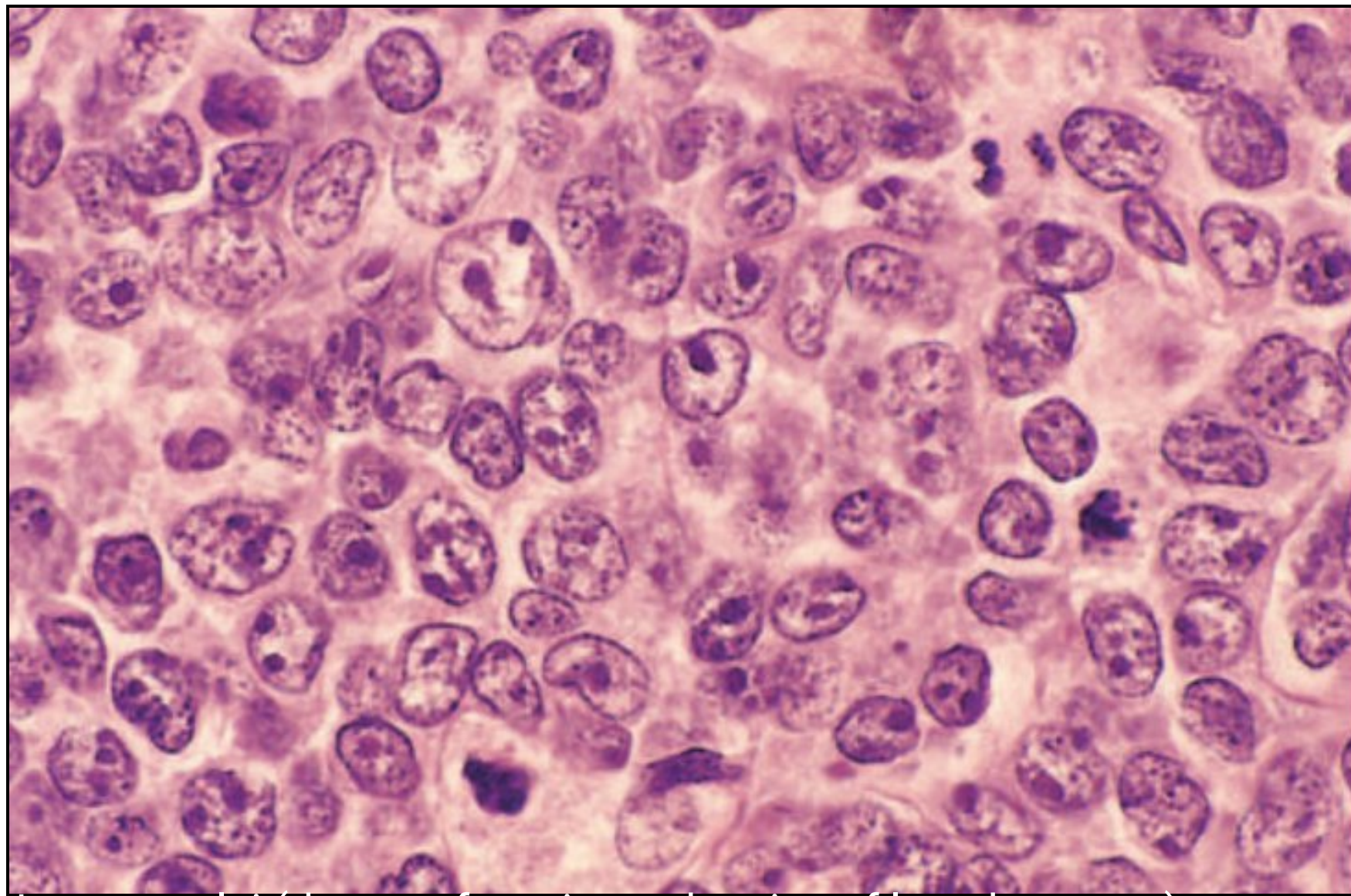
Morphology:

Neoplastic proliferation of large B cells that grow diffusely in sheets.

DLBL (diffuse large B-cell lymphoma)

Primary effusion lymphoma:

Special type of DLBL, occurs in old patients with AIDS characterized by pleural effusion and ascites (HHV-8).



Burkitt lymphoma

Neoplastic proliferation of intermediate-sized B cells (CD20 +).

1/3 Childhood NHL

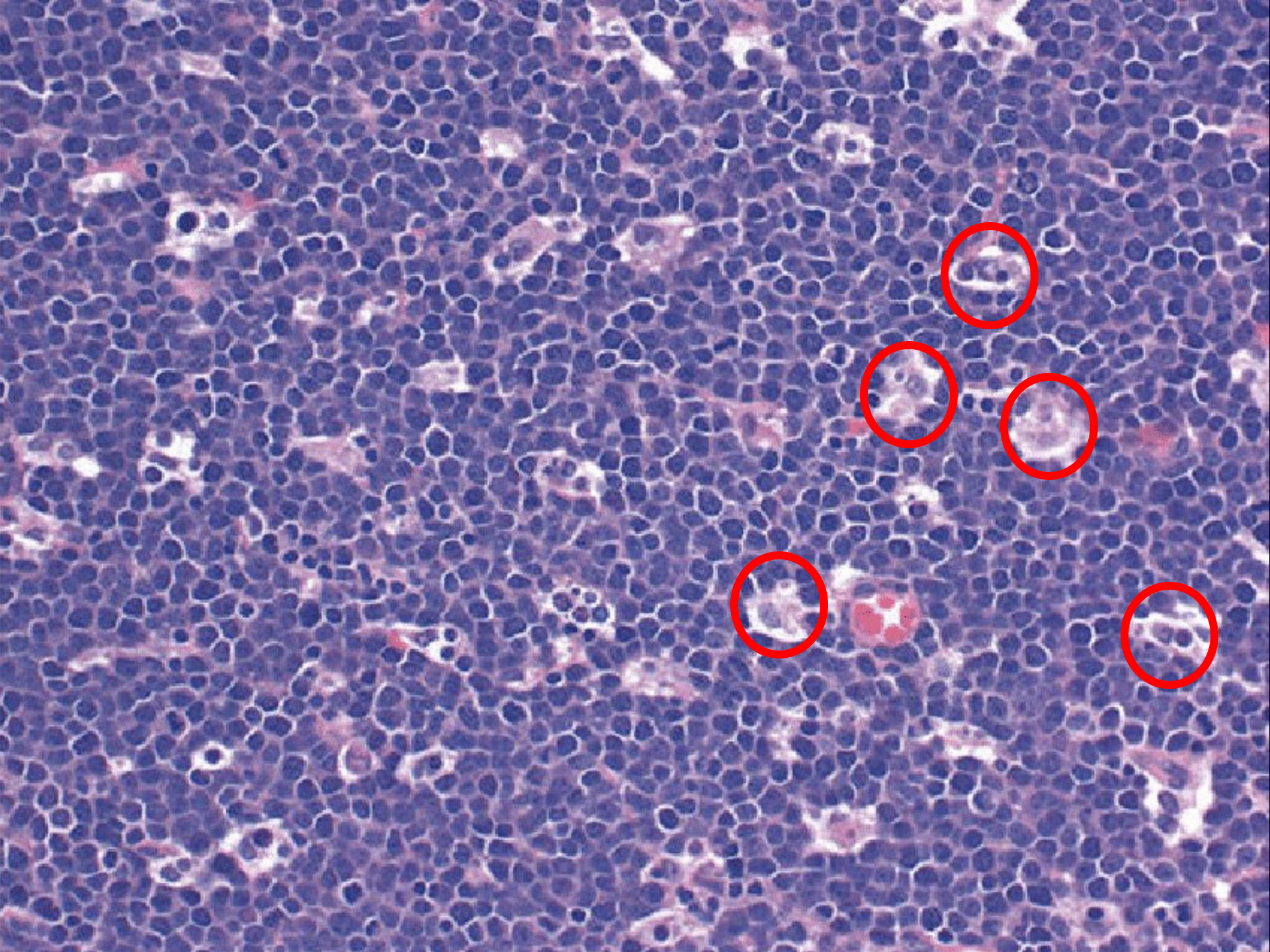
Classically presents as an extranodal mass in a child or young adult.

High grade lymphoma

Burkitt lymphoma

Karyotyping: t(8;14)
(C-myc, Ig)

IPT: CD20,CD10,BCL6



Immunodeficiency related BL

HIV +ve pt

Varies .35%

Sporadic BL	Endemic BL
Europe North America	Equatorial Africa
15%	95%
Abdominal	Face/neck Orbital, Jaw

Geography

EBV

Common presentation





Categorization of Lymphoma

