World Health Organization Classification of Neoplastic Diseases of the Hematopoietic And Lymphoid Tissues

The WHO attempts to establish uniform Classification schemes … in order to facilitate International collaborations and comparison of Epidemiological, clinical, and biological data.

Participation : Oncologists and Hematopathologists

World Health Organization Classification of Neoplastic Diseases of the Hematopoietic And Lymphoid Tissues

Based on the Principles of REAL Classification

WHO Classification of Lymphomas- B cell type

Map and Guide for Future Clinical and Investigational Studies:

- Historical background
- REAL classification concepts
- WHO Classification
- Biology and Technology
- Entities

Hernani Cualing MD

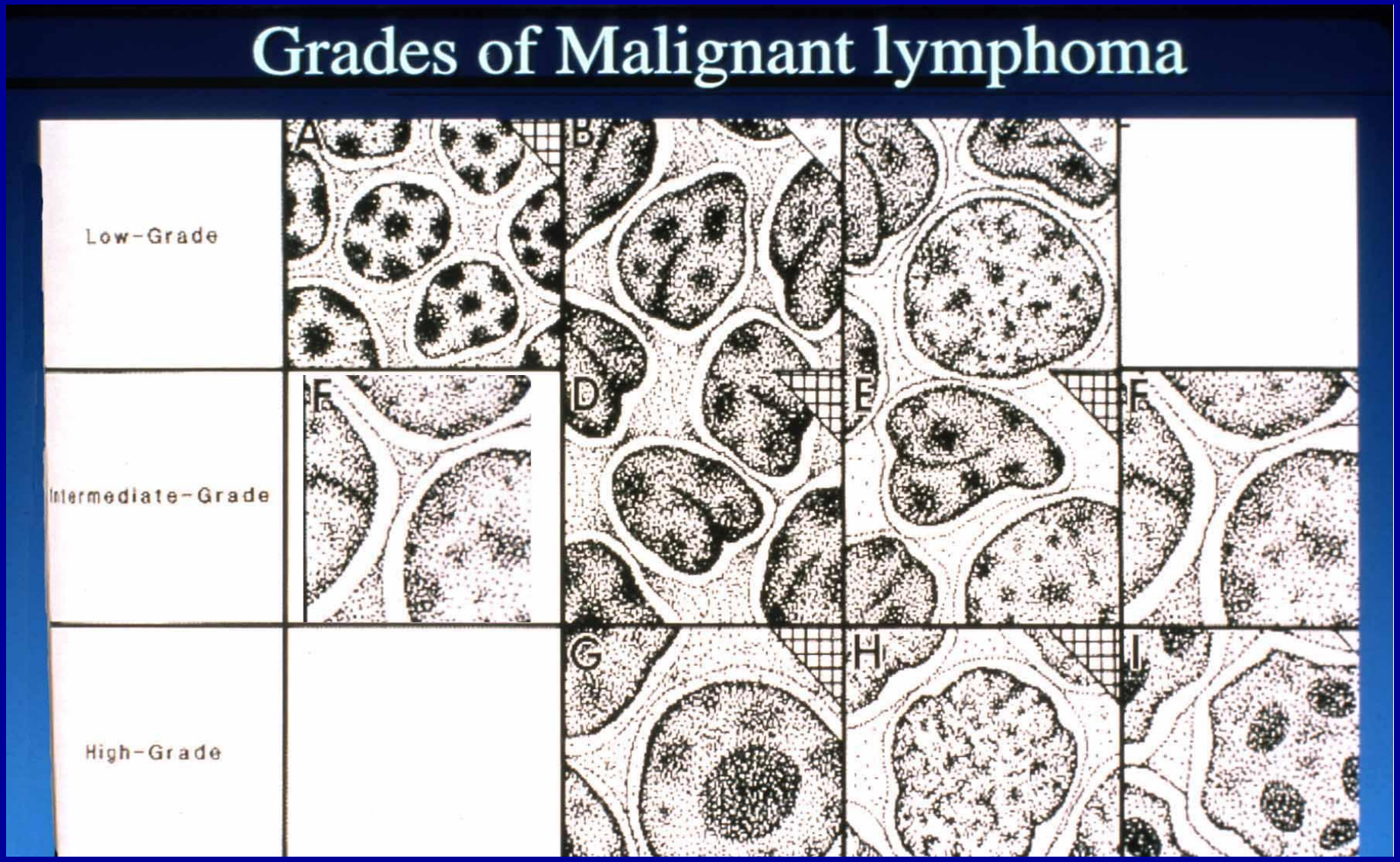
Historical Background

- **1970's -six classifications, 4 in use**
  - Rappaport (US)
  - Lukes-Collins (US)
  - Kiel (Europe)
  - BNLI(UK)
- **Meetings held in London(73), Florence (74), Airlie, VA (75) failed to produce consensus**
- **DeVita (NCI) sponsored a study to evaluate schemes**
- **Working Formulation (1982) was based on clinical outcome data from the study-**
  - **Rappaport scheme with altered terminology**
  - **Rejected by Lukes, Lennert**

Evolution of Lymphoma Classification

- **Rappaport: descriptive using both cytology and architecture**
- **Working Formulation: Stratify lymphomas of diverse types according to clinical outcome**
  - Most categories were heterogeneous (Diffuse small cleaved, diffuse mixed, diffuse large cell)
  - morphology based, reproducibility poor
- **Kiel: cytologically based on putative cell of origin; intended for nodal lymphomas**
  - extrapolation to extranodal lymphomas not accurate
  - cytology was misleading in classification of T cell lymphomas

Morphologic Classification



WORKING FORMULATION

May Add

LOW GRADE

- Malignant lymphoma, small lymphocytic
- Malignant lymphoma, plasmacytoid lymphocytic
- Malignant lymphoma, follicular predominantly small cleaved cell
- Malignant lymphoma, follicular, mixed small cleaved and large cell

MALT/
Monocytoid B-cel
Mantle zone

INTERMEDIATE GRADE

- Malignant lymphoma, follicular, predominantly large cell
- Malignant lymphoma, diffuse, small cleaved cell
- Malignant lymphoma, diffuse, mixed small, large cell
- Malignant lymphoma, diffuse, large cell

Intermediate lym
Lennert's lympho

HIGH GRADE

- Malignant lymphoma, large cell, immunoblastic
- Malignant lymphoma, lymphoblastic
- Malignant lymphoma, small non-cleaved cell

Large cell anaplas

MISCELLANEOUS

- Composite malignant lymphoma
- Mycosis fungoides
- Extramedullary plasmacytoma
- Unclassifiable
- Other

Impetus for REAL Classification

- In 1994, both WF and Kiel were in use
  - Persistent lack of international consesus
- New entities defined not recognized in either classification
  - MALT lymphomas, most extranodal T/ NK cell lymphomas
- Emerging basis for true international consensus
  - Immunophenotypic and molecular criteria existed to define disease entities

Impetus for REAL Classification

- Deficiencies present in both major schemes
- Working Formulation
  - Lymphoma classification based on clinical outcome
  - Lumped together diseases sharing similar cell size and cytology into single categories, irrespective of cell type or lineage

– Kiel Classification
  - Designed for nodal lymphomas only
  - Cytologically based without use of clinical data

REAL/WHO Classification

- REAL Classification - new paradigm
- Focus was on identification of REAL disease entities
- Based on building an international consensus
- Utilized data from published literature

Principles of REAL/WHO Classification

- Include all lymphoid neoplasms
  - Nodal and extranodal, HL and NHL
  - Lymphomas and lymphoid leukemias
- Broad groupings:
  - B, T cell, Hodgkin's
- Two major differentiation stages
  - Precursor and Mature lymphoid

REAL/WHO Classification

- **Each disease is a distinct entity based on constellation of clinical and laboratory features**
  - **Morphology**
  - **Immunophenotype**
  - **Genetic features**
  - **Clinical presentation and course**
- **Site of involvement is often a signpost for important biologic distinction**
- **Distinguishes between cytologic grade from clinical aggressiveness**

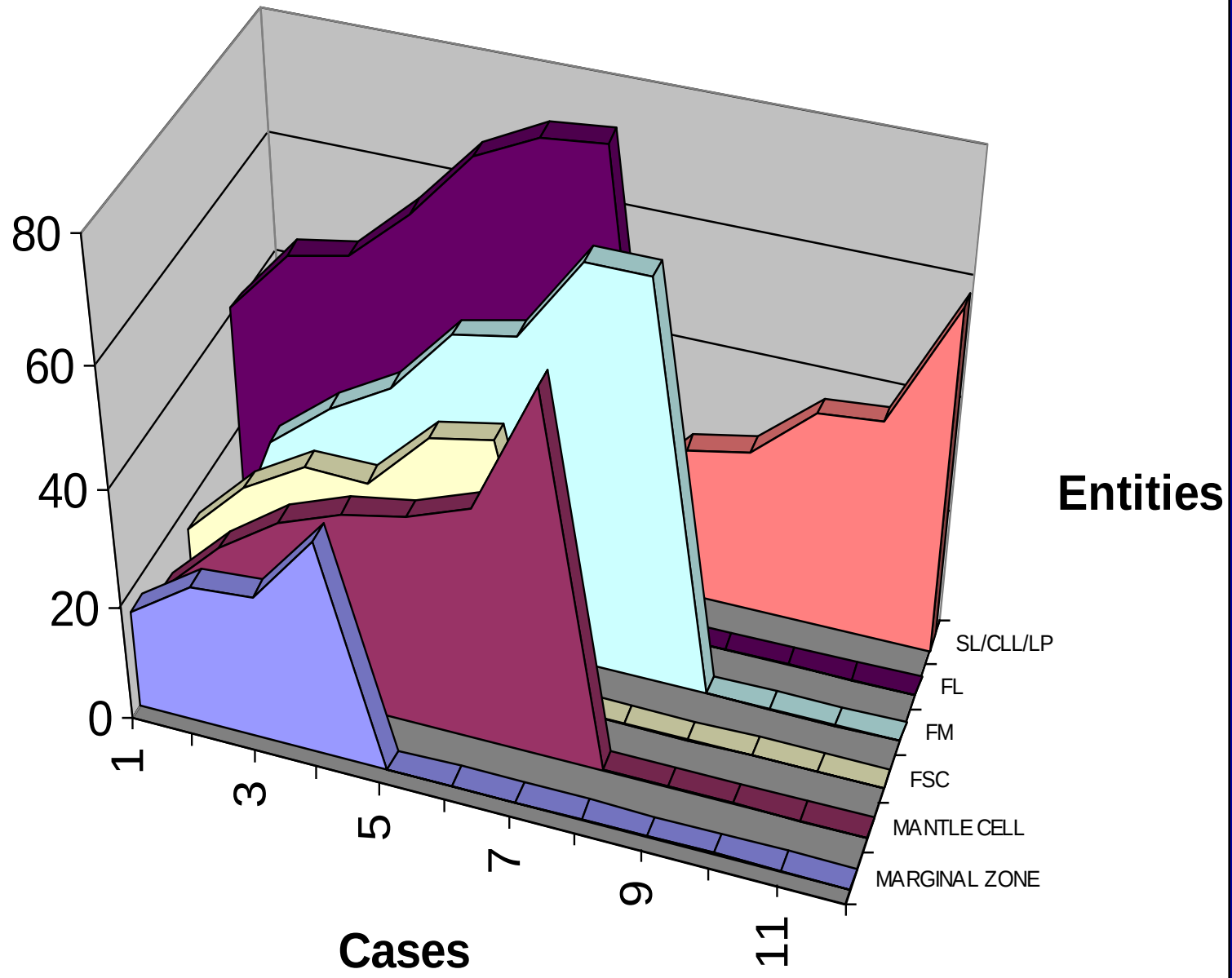
REAL/WHO Classification

- Histologic grade
  - Based on cytologic features such as cell size, nuclear features
  - Proliferation fraction (mitosis, Ki67)
- Clinical aggressiveness
  - Does not always correlate with histologic grade
  - Example: mantle cell lymphoma, Anaplastic large cell lymphoma

REAL/WHO Classification: Grade

- **Many lymphomas have a range of histologic grade and aggressiveness**
  - **Follicular lymphomas**
  - **Mantle cell, Small lymphocytic/CLL**
  - **Adult T-cell lymphomas /leukemias**

Figure2. CD71TfR Expression in NHL's



WHO Classification

- Histologic/cytologic grade
  - –Based on cytologic features such as cell size, nuclear features
  - –Proliferation fraction (mitosis, Ki67,CD71)

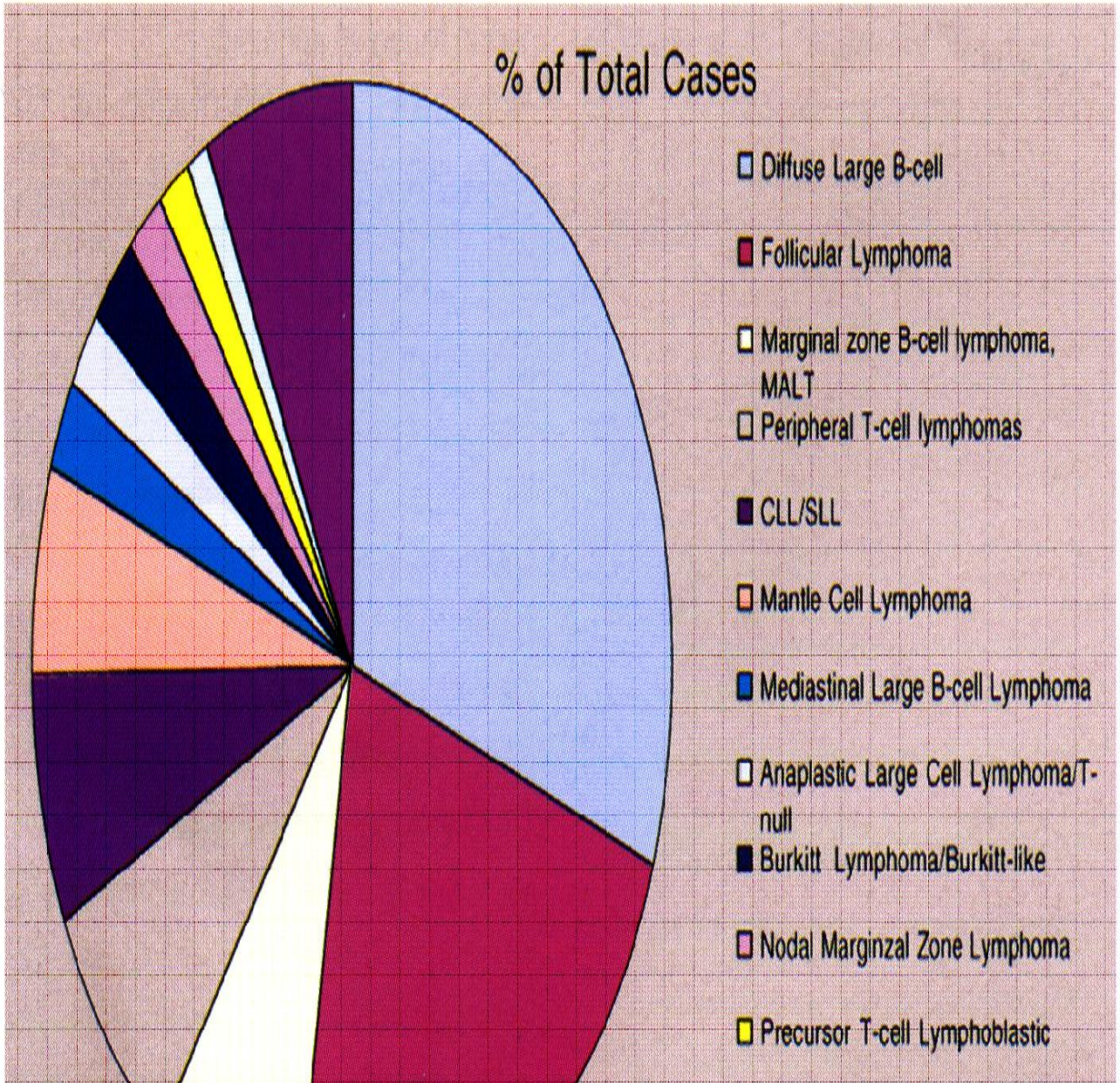
  - –Markers (biologic) to diagnose and to prognosticate are commonly used as a standard of practice

Contribution of Immunophenotype to Diagnosis (Intl Study… Blood, 89:3909, 1997)

Increased Diagnostic Accuracy with and without Immunophenotypic studies (%)

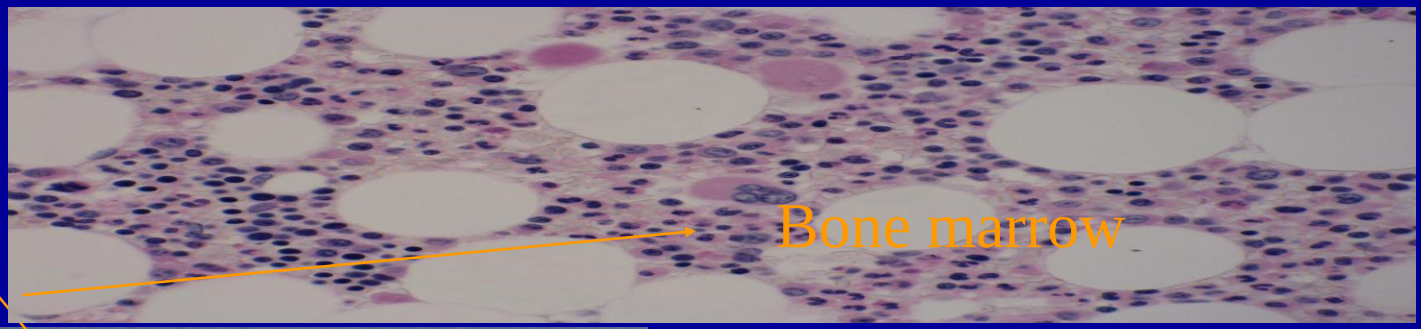
Mantle cell Lymphoma	+10
Diffuse large BCL	+14
Precursor LBL	+35
ALCL, T/Null	+39
Peripheral TCL	+45
FL, CLL, MALT, Burkitt's	< 5

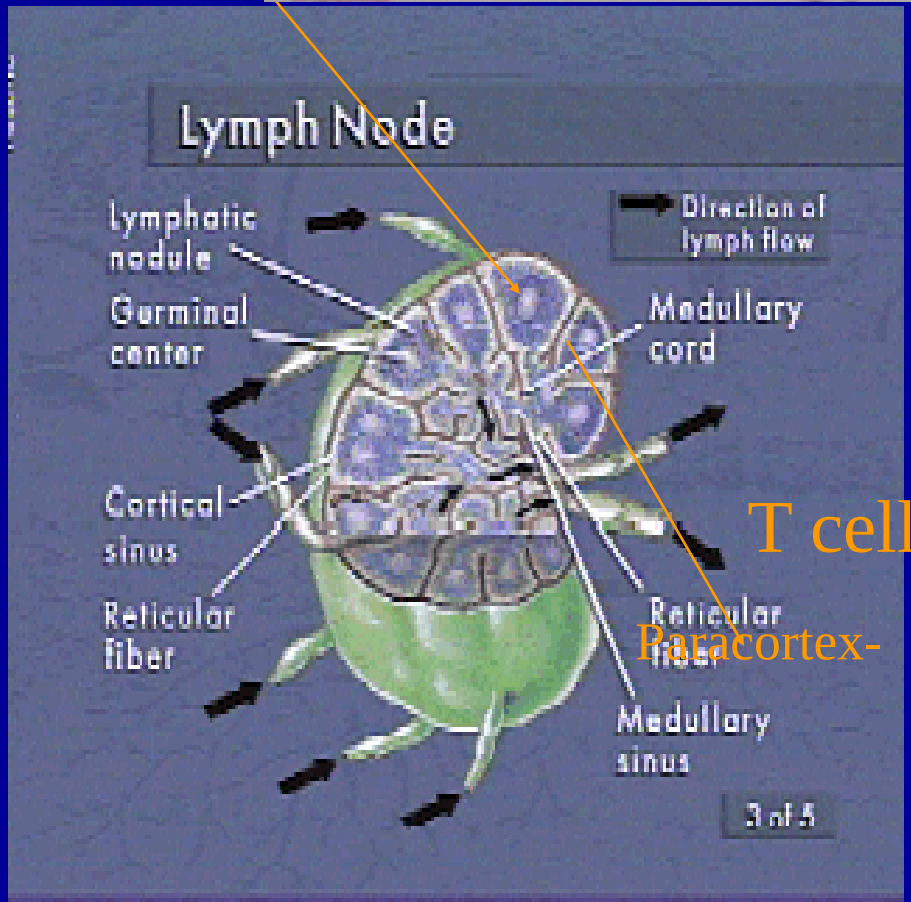
Diagnosis	% of total cases
Diffuse large B-cell	30.6%
Follicular lymphoma	22.1%
Marginal zone B-cell lymphoma, MALT	7.6%
Peripheral T-cell lymphomas (PTL)	7.6%
PTL, NOS	3.7%
Nasal NK/T	1.4%
Angioimmunoblastic T-cell	1.2%
Enteropathy-type	<1
Hepatosplenic	<1
Adult T-cell leukaemia/lymphoma*	<1
CLL/SLL	6.7%
Mantle cell lymphoma	6.0%
Mediastinal large B-cell lymphoma	2.4%
Anaplastic large cell lymphoma/T-null	2.4%
Burkitt lymphoma/Burkitt-like	2.5%
Nodal marginal zone lymphoma	1.8%
Precursor T-cell lymphoblastic	1.7%
Lymphoplasmacytic lymphoma	1.2%
Other types	7.4%



Sites of lymphocyte development

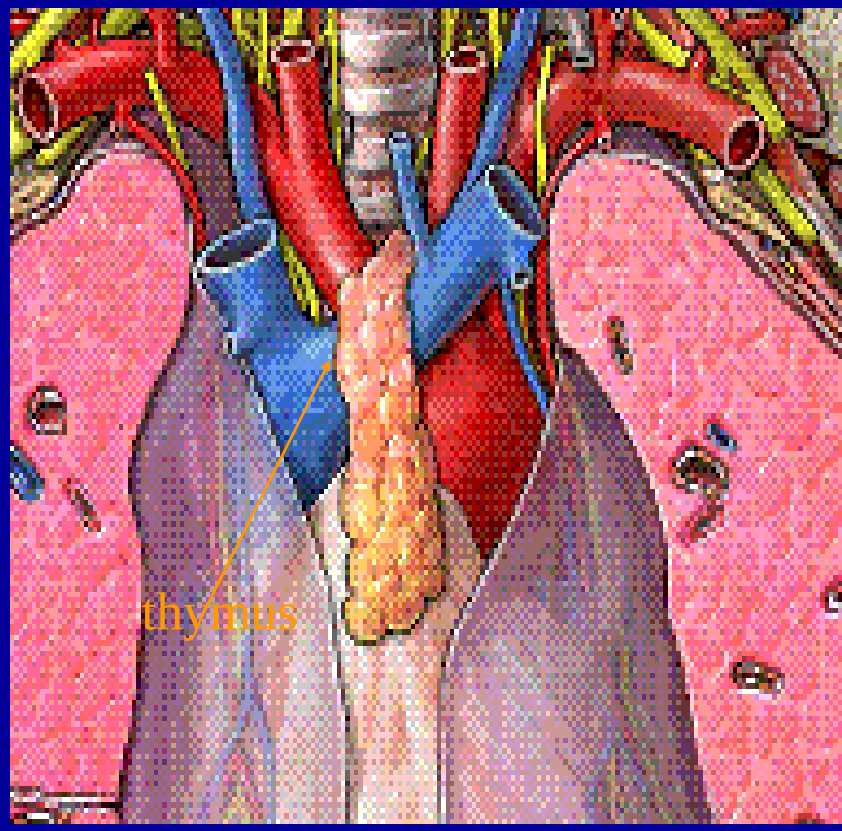
- B cell cortex-

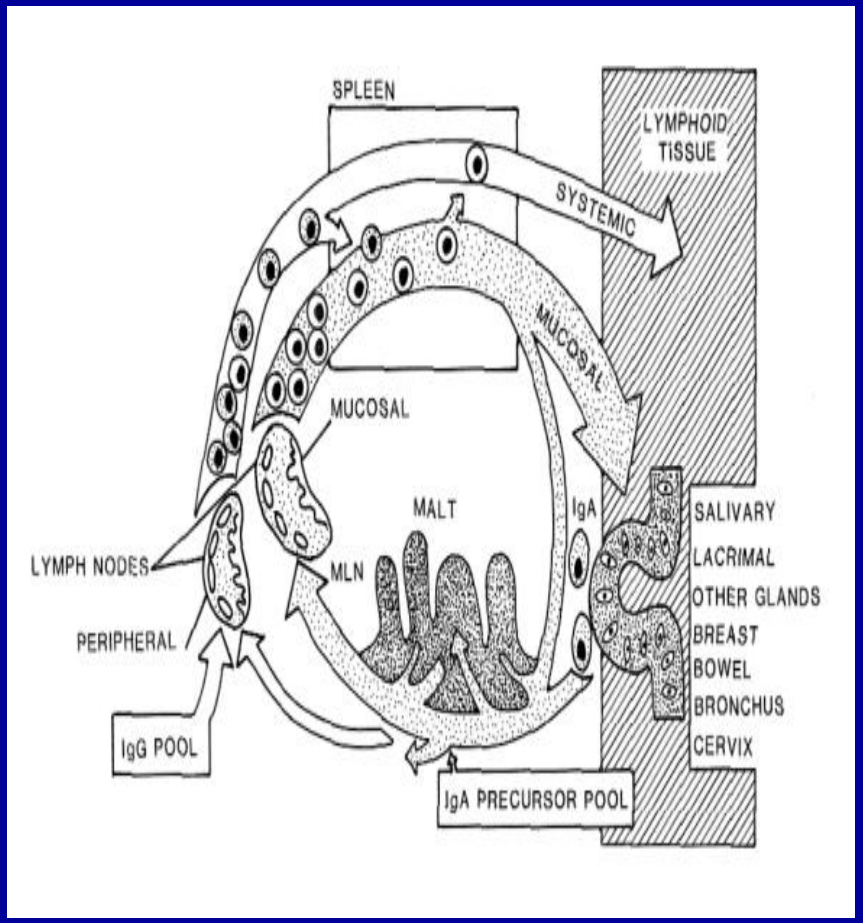




T cell

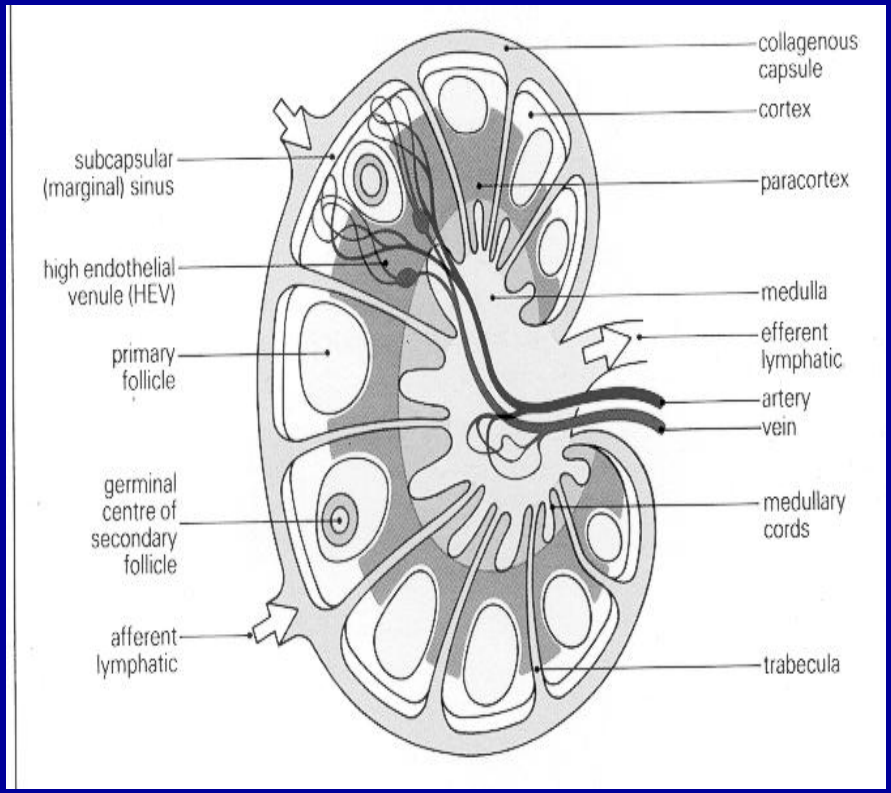
Paracortex-



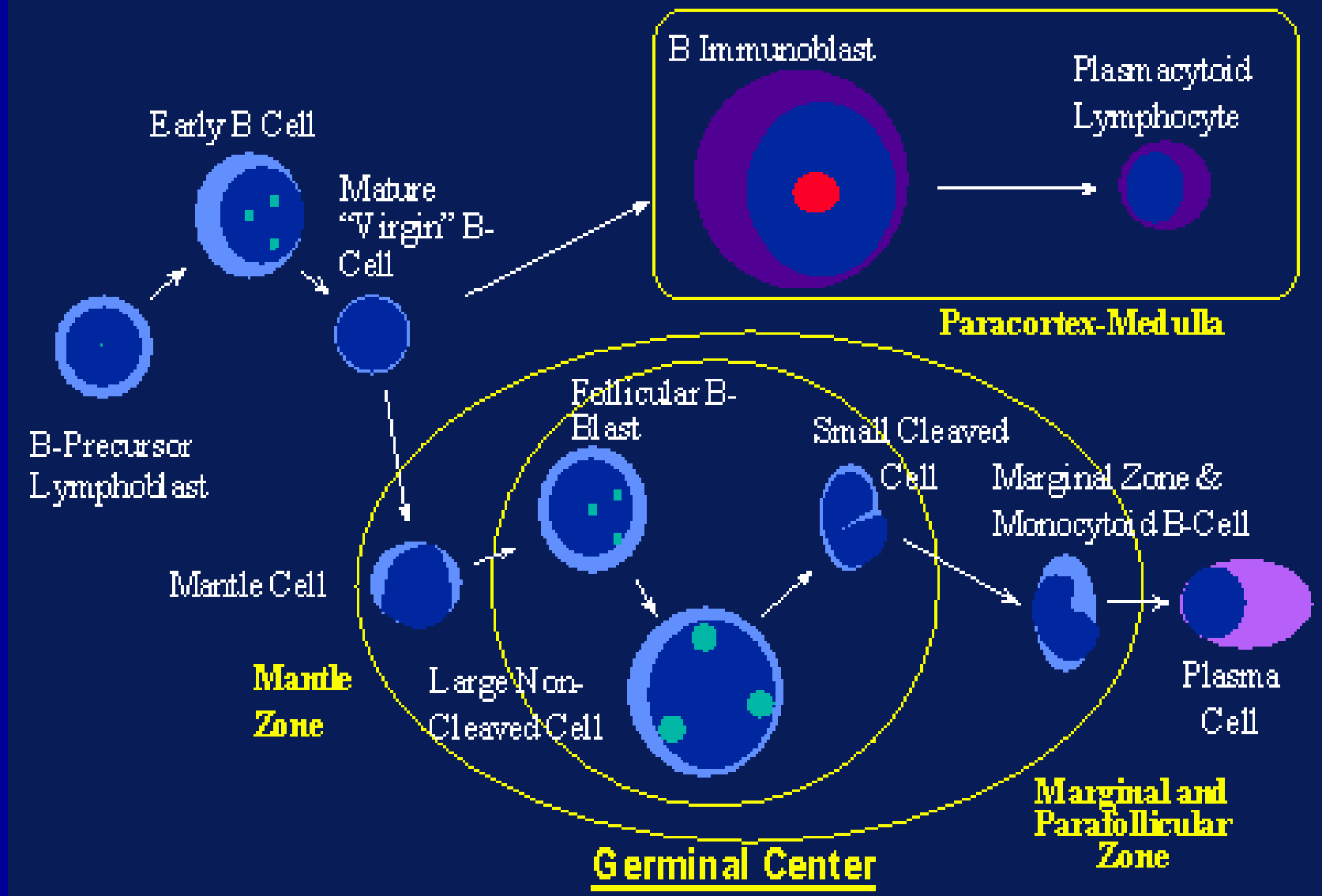


NODAL AND EXTRANODAL PATHWAYS

DUAL SUPPLY IN LYMPH NODES

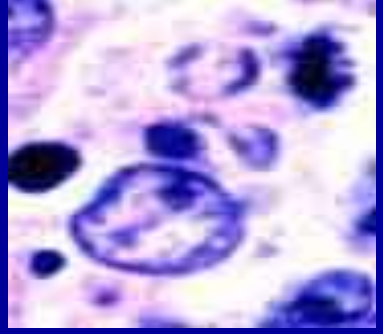


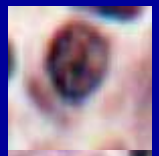
B-Cell Ontogeny

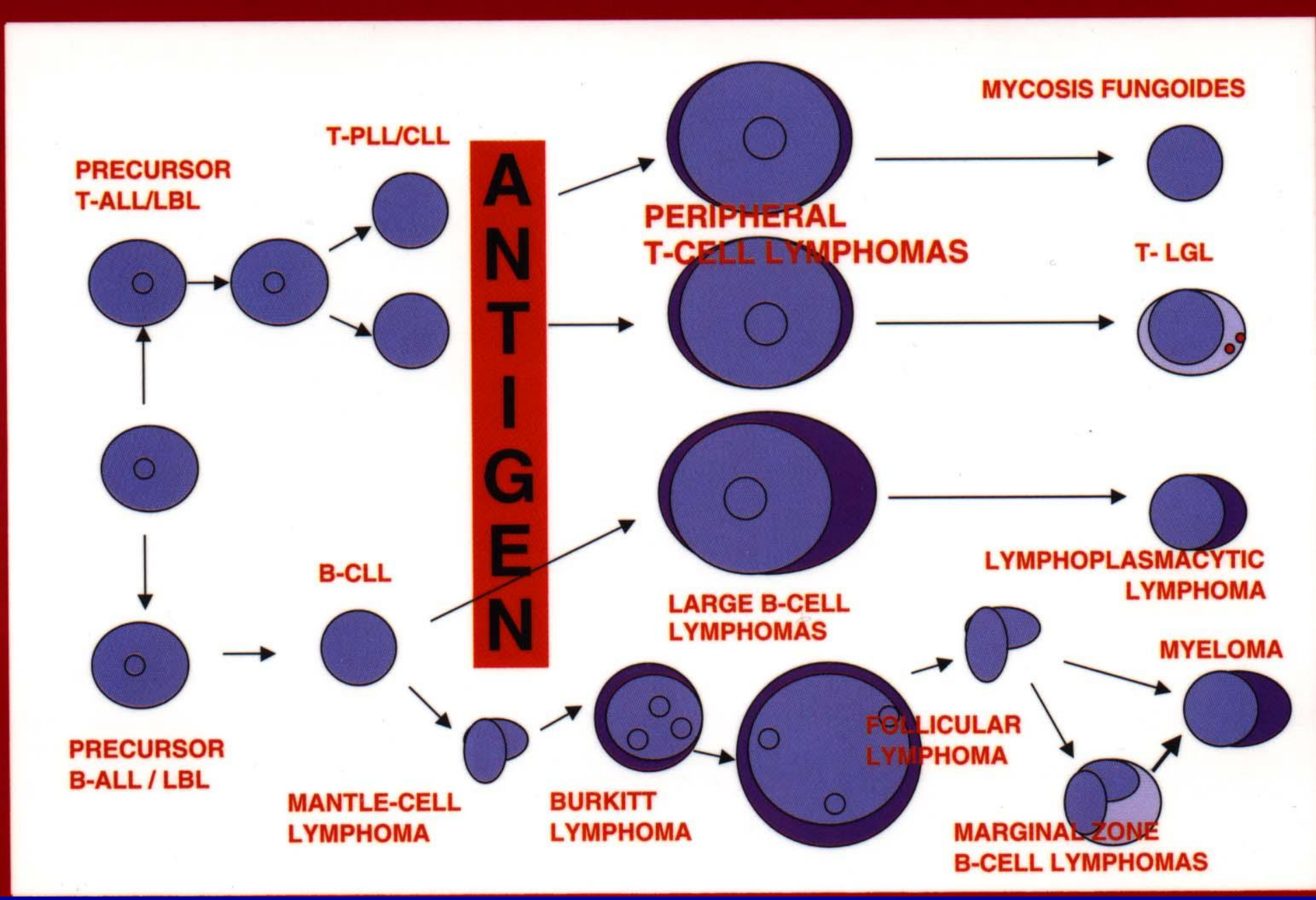


Histiocyte

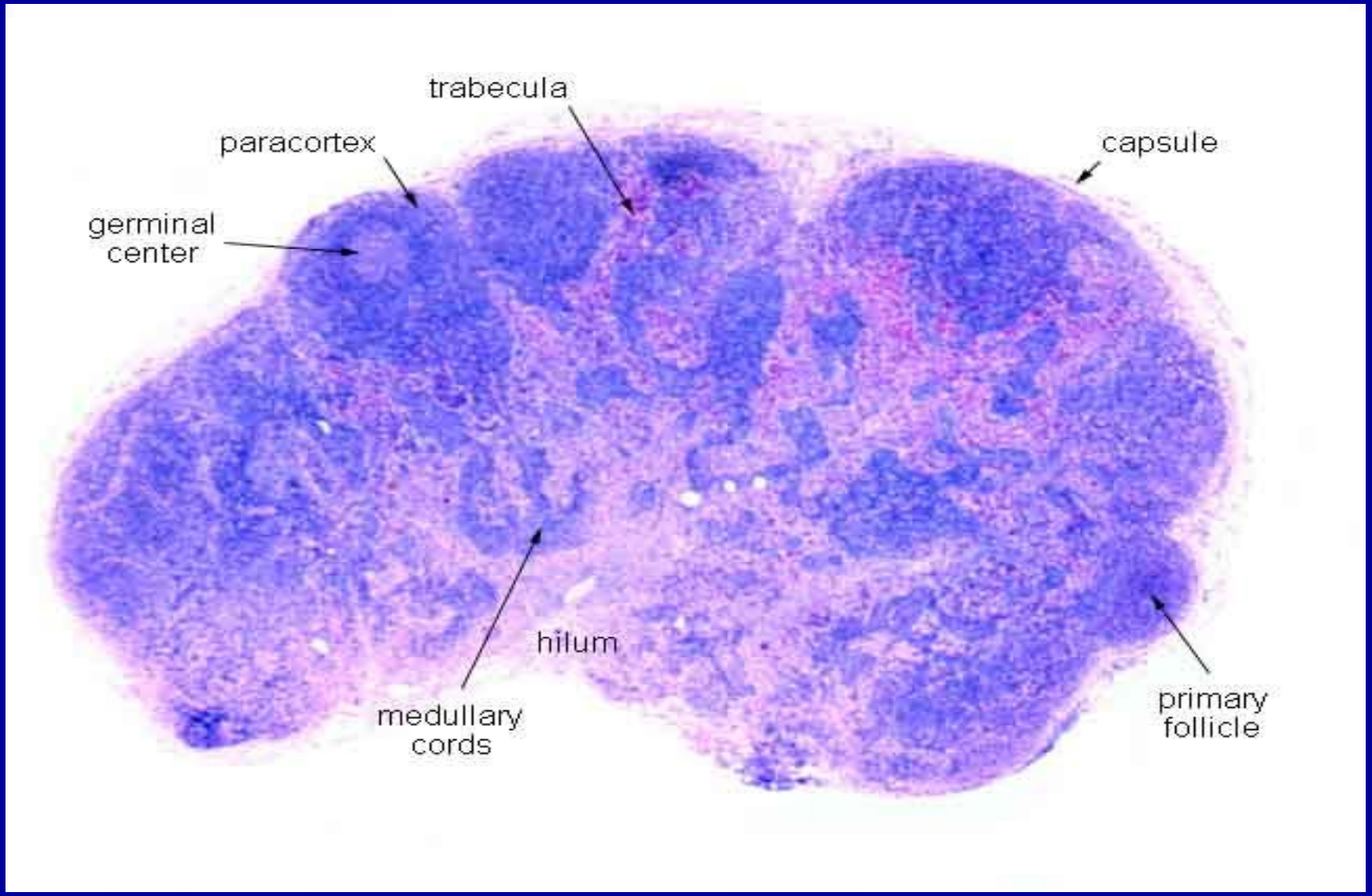
Small Cells	Intermediate Cells	Large Cells
 Small round (Lymphocyte)	 Lymphoblast (Convoluted Lymphoblast)	 Large non-cleaved (Centroblast)
 Small cleaved (Centrocyte)	 Small non-cleaved (Burkitt's lymphoblast)	 Immunoblast (Immunoblast)
 Plasmacytoid small lymph (Immunocyte)		
 Monocytoid small lymph (Monocytoid lymph)		

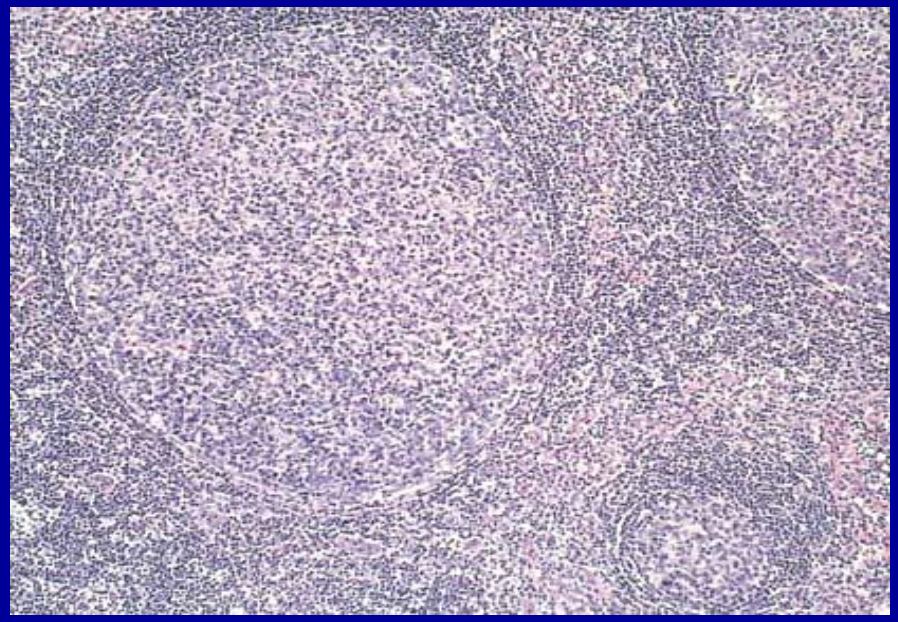


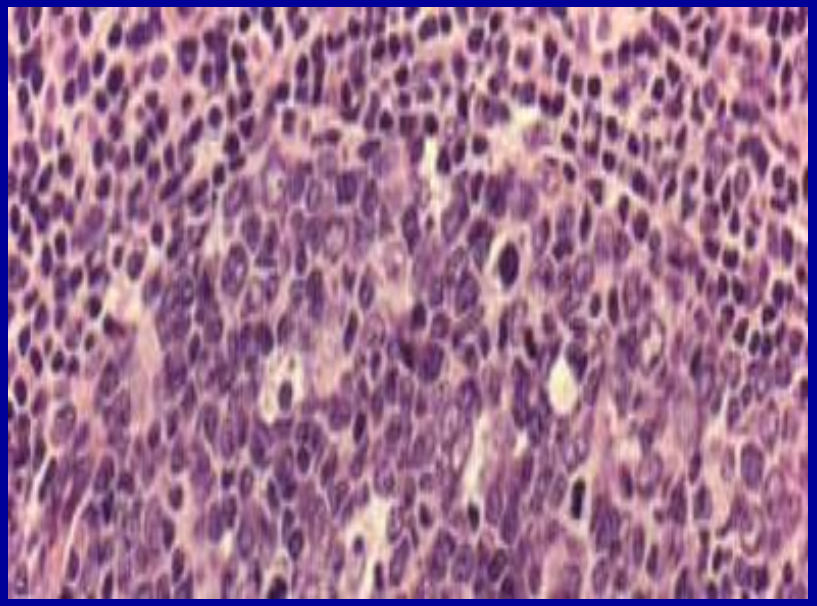


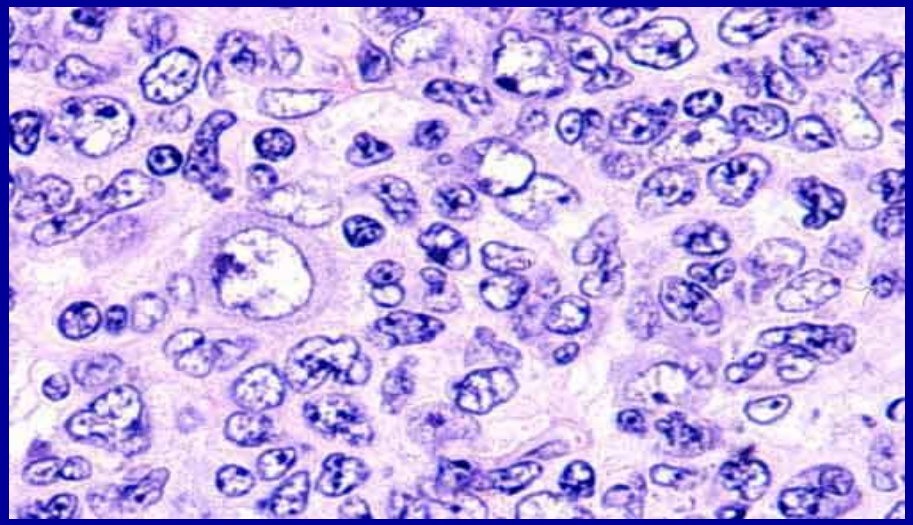

MYCOSIS FUNGOIDES
T-PLL/CLL
PRECURSOR
T-ALL/LBL
ANTIGEN
PERIPHERAL
T-CELL LYMPHOMAS
T- LGL
B-CLL
LYMPHOPLASMACYTIC
LYMPHOMA
LARGE B-CELL
LYMPHOMAS
MYELOMA
FOLLICULAR
LYMPHOMA
PRECURSOR
B-ALL / LBL
MANTLE-CELL
LYMPHOMA
BURKITT
LYMPHOMA
MARGINAL ZONE
B-CELL LYMPHOMAS

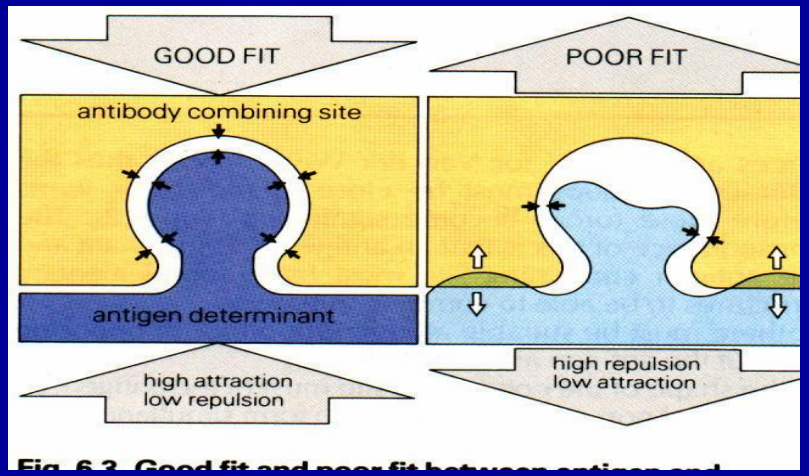
Normal lymph node architecture











Polarity-light and dark zones

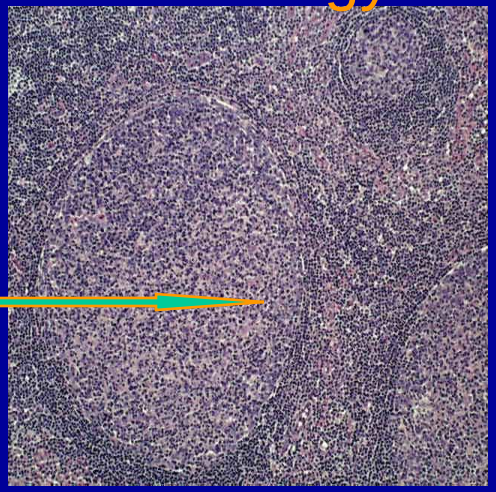
Good fit-live
Poor fit-die

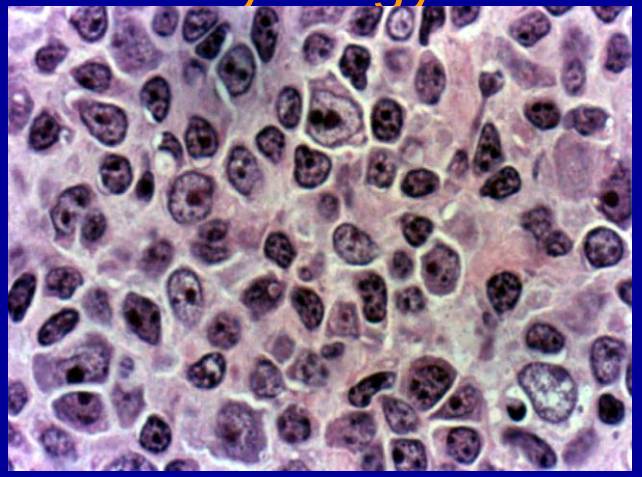
Histologic findings

histology

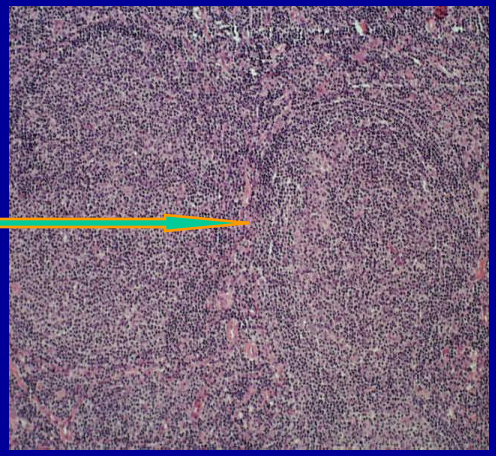
cytology

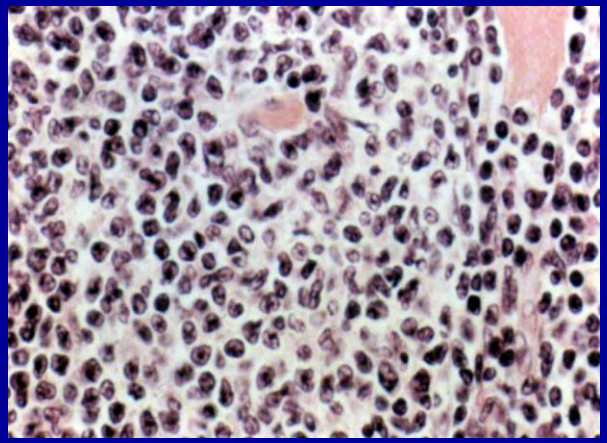
- TISSUE BIOPSY
  - morphology
    - polarized reactive follicles





    - homogeneous follicular lymphoma





The malignant lymphomas

- Definition: malignant monoclonal neoplasms of lymphocytes which can arise at nodal and extranodal sites.
- Presentation:
  As tumors arising out of organs of the immune system, they present as enlargement of lymph nodes, spleen, and extranodal lymphoid tissues.

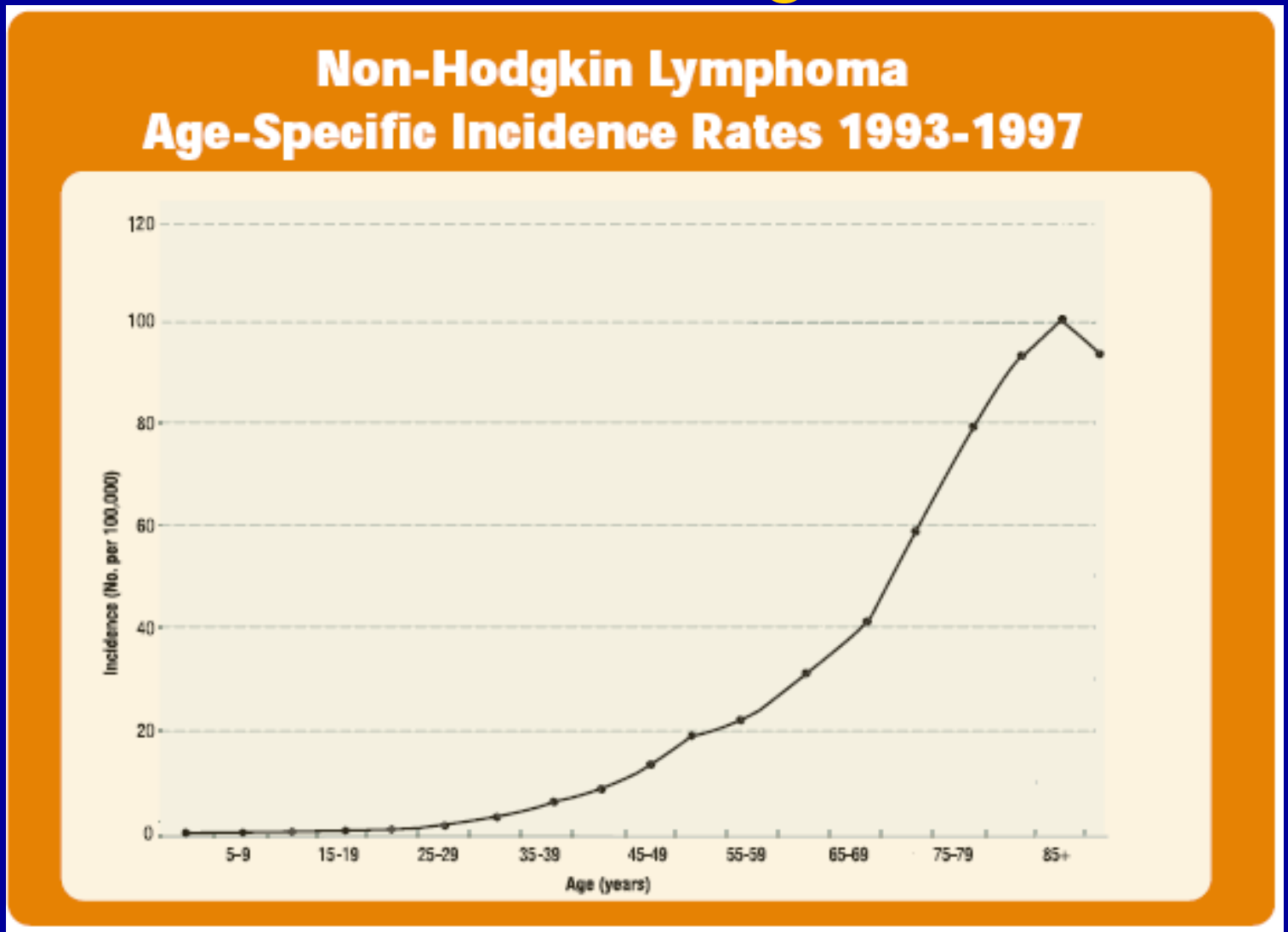
- Histologic Patterns: Nodular or diffuse

Many lymphomas have leukemic counterparts

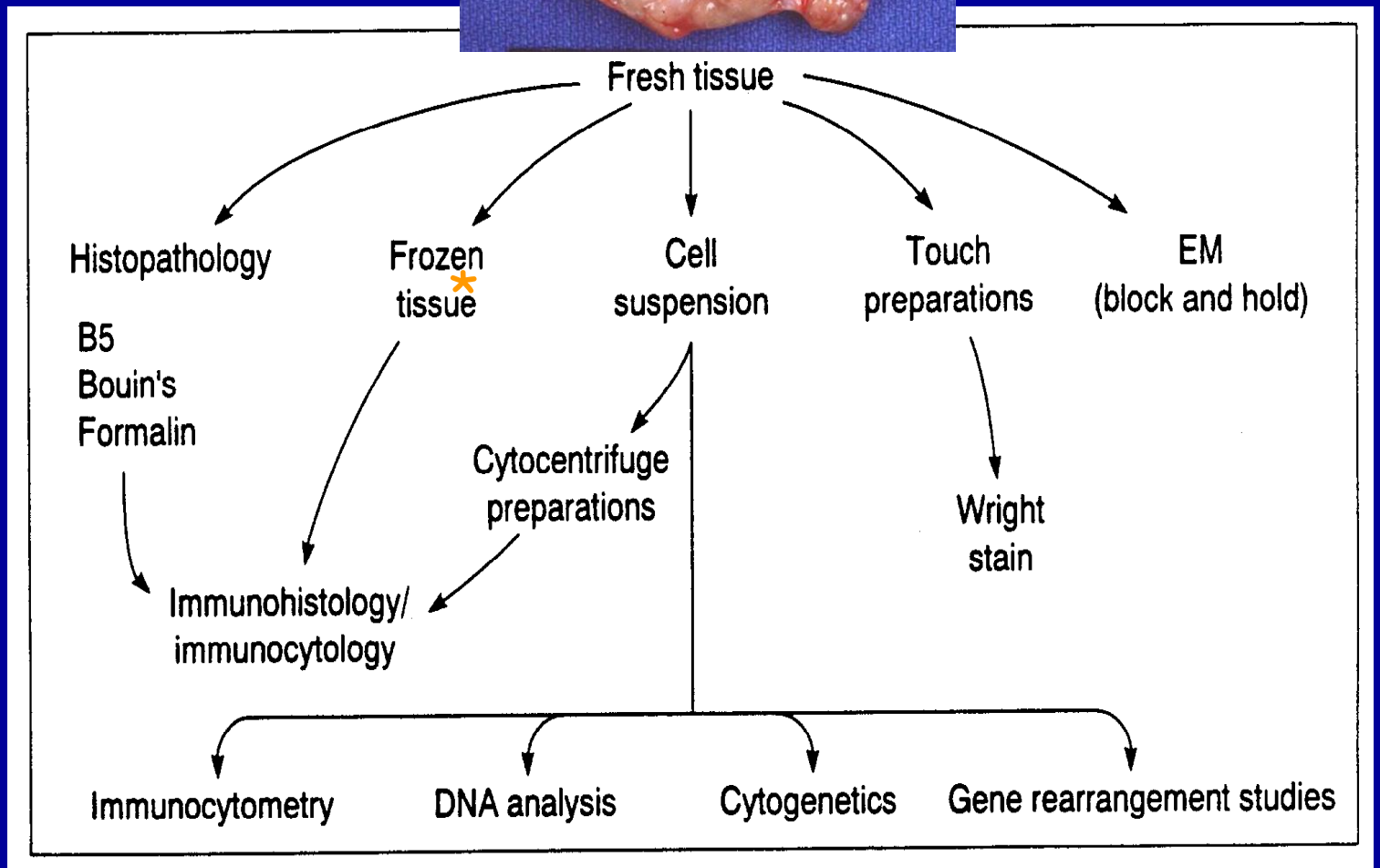
Causes and Risk Factors Non Hodgkin Lymphomas: **Annual incidence of lymphoma in North America has nearly doubled over the last 35 years**

- **1. Immune deficiencies:**
  - **Increased patients with organ transplants and with immune deficiencies, ie. HIV, congenital**
- **2. Chemicals:**
  - **herbicides and pesticides**
- **3. Infectious agents:**
  - **Epstein Barr Virus- Burkitt Lymphoma**
  - **Human T lymphotropic virus- Adult T cell lymphoma**
  - **Helicobacter pylori- gastric lymphoma**
  - **Human immunodeficiency virus (HIV), 50 and 100 x incidence**
- **4. Age & Race : Since lymphoma is disease of old people and higher in caucasian**

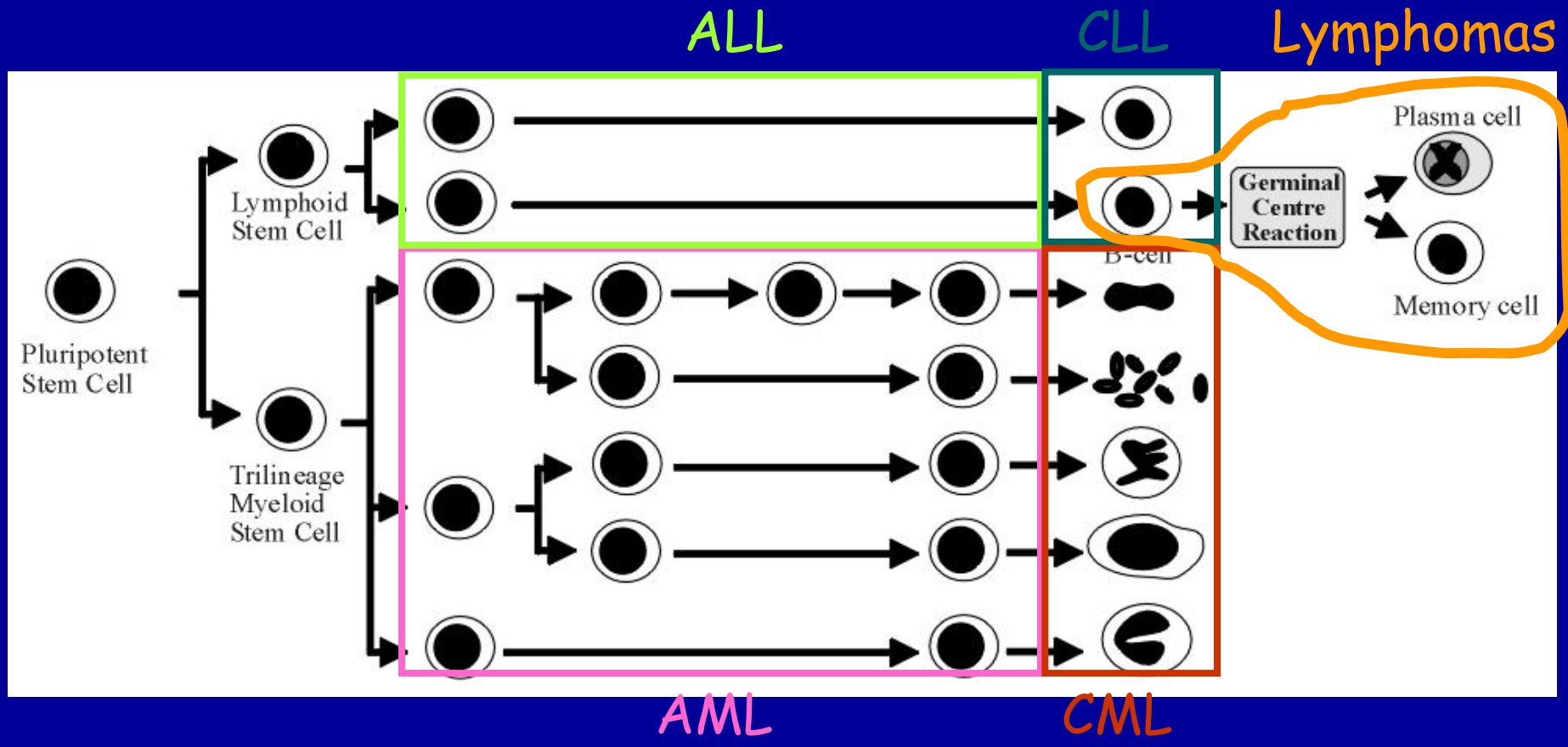
–Lymphomas incidence correlate with older age



DIAGNOSIS-HANDLING OF A LYMPH NODE BIOPSY

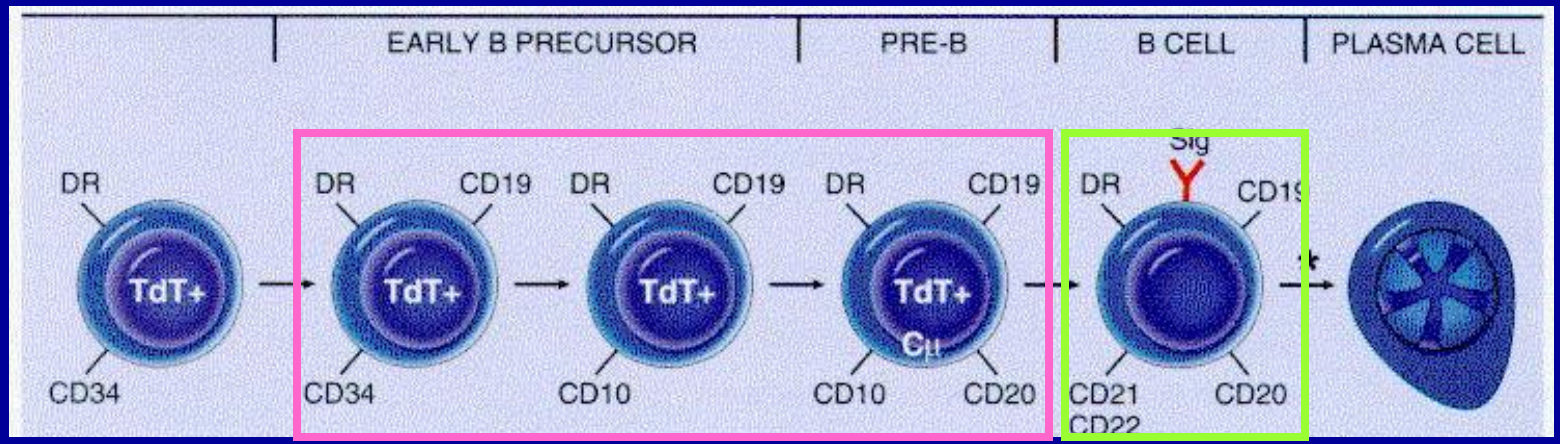


Lymphomas


ALL
CLL
Lymphomas
Lymphoid Stem Cell
Pluripotent Stem Cell
Trilineage Myeloid Stem Cell
B-cell
Germinal Centre Reaction
Plasma cell
Memory cell
AML
CML

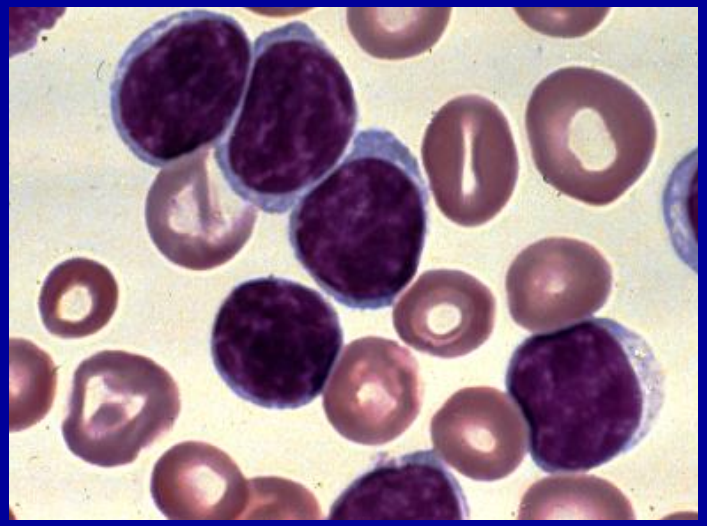
B-Lineage Lymphopoiesis

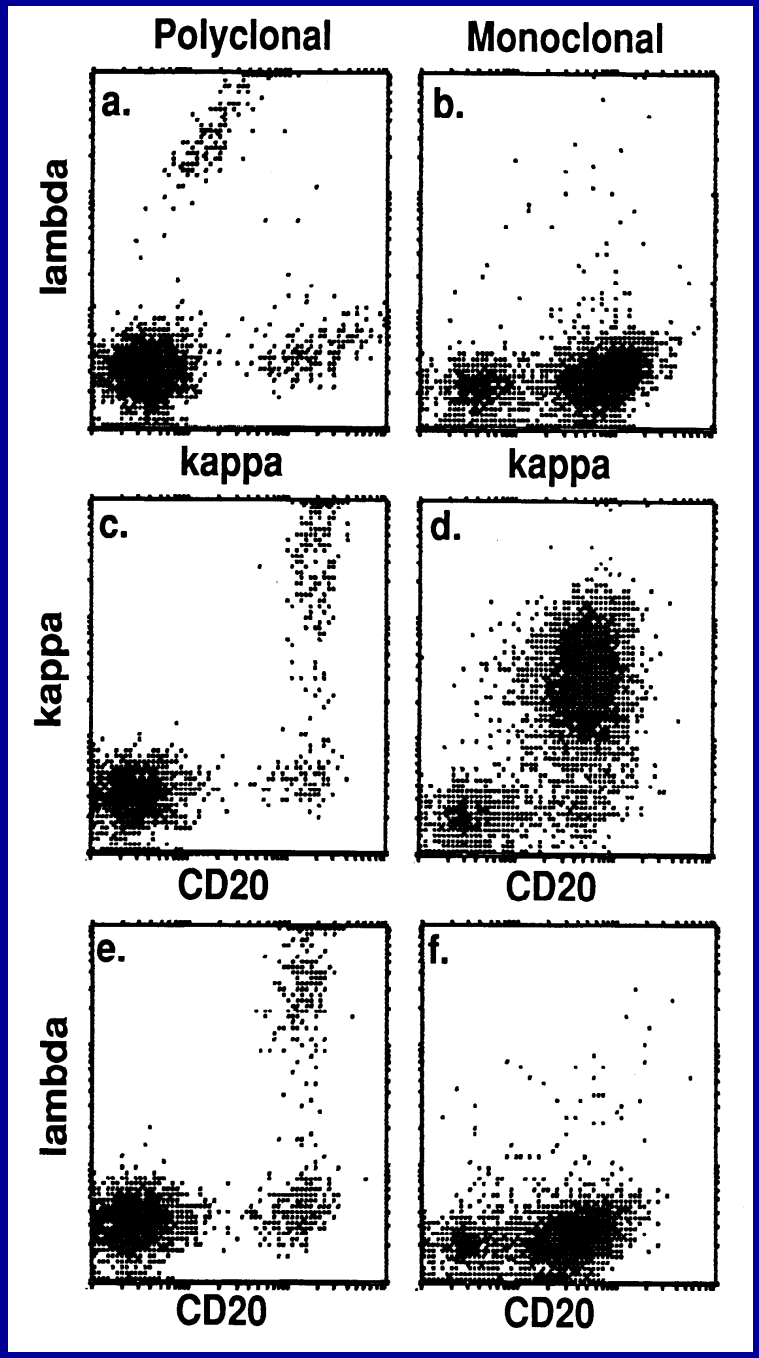
Morphology / Immunophenotyping / Molecular Studies



"Blasts"

"Mature" Lymphocytes

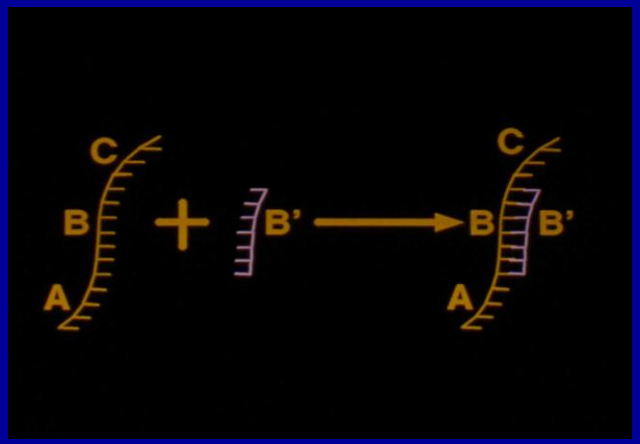




DEMONSTRATION OF B-CELL CLONALITY BY FLOW CYTOMETRY

(Remember that no flow cytometric clonality assay exists for T cell malignancies.)

GENE REARRANGEMENT



Clonality

	Ig gene	Tcr gene
• B cell neoplasms	+	-
• T cell neoplasms	-	+
• Benign proliferation	-	-

T CELL RECEPTOR

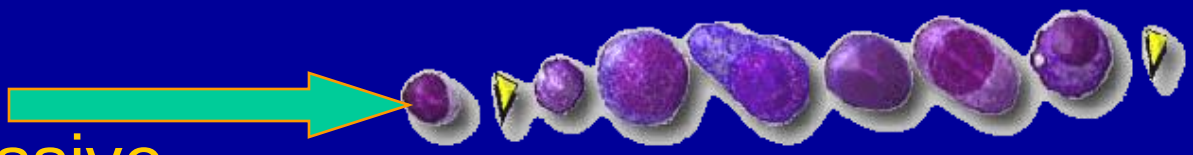
PATHOGENETIC INSIGHTS BASED ON A DISEASE-ORIENTED APPROACH TO LYMPHOMA CLASSIFICATION

Lymphoma	Pathogenesis/ Cofactor
Burkitt lymphoma	EBV, c-myc; t(8;14)
Adult T cell leuk/ lymphoma	HTLV-1
Gastric MALT lymphoma	Helicobacter, genetics
Nasal T/NK cell lymphoma	EBV, genetics
Mantle cell lymphoma	Bcl-1/Cyclin D1; t(11;14)
Follicular lymphoma	bcl-2 rearrangement; t(14;18)
Anaplastic Ki-1 lymphoma	NPM/ALK; t(2;5)

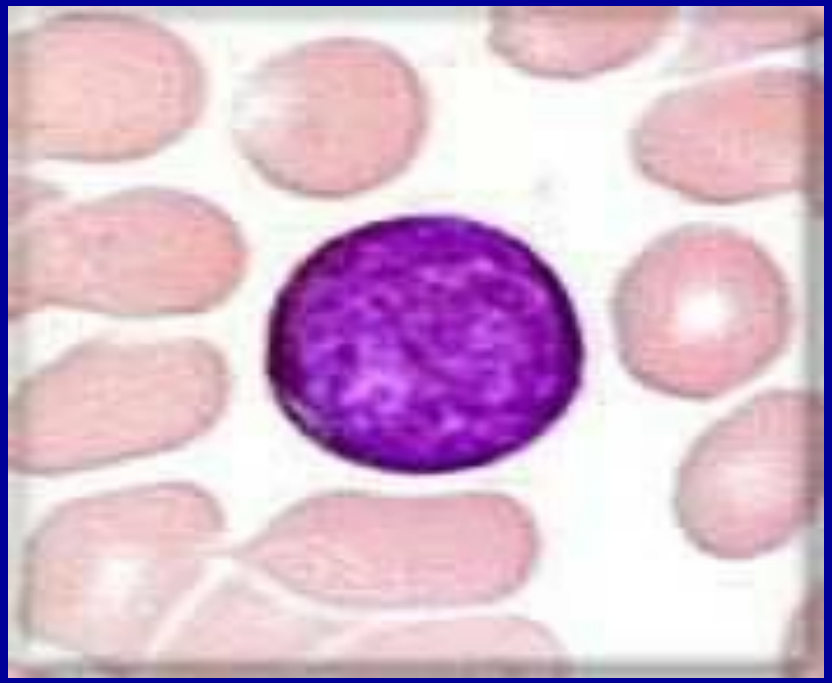
PRINCIPAL METHODS OF LYMPHOMA DIAGNOSIS

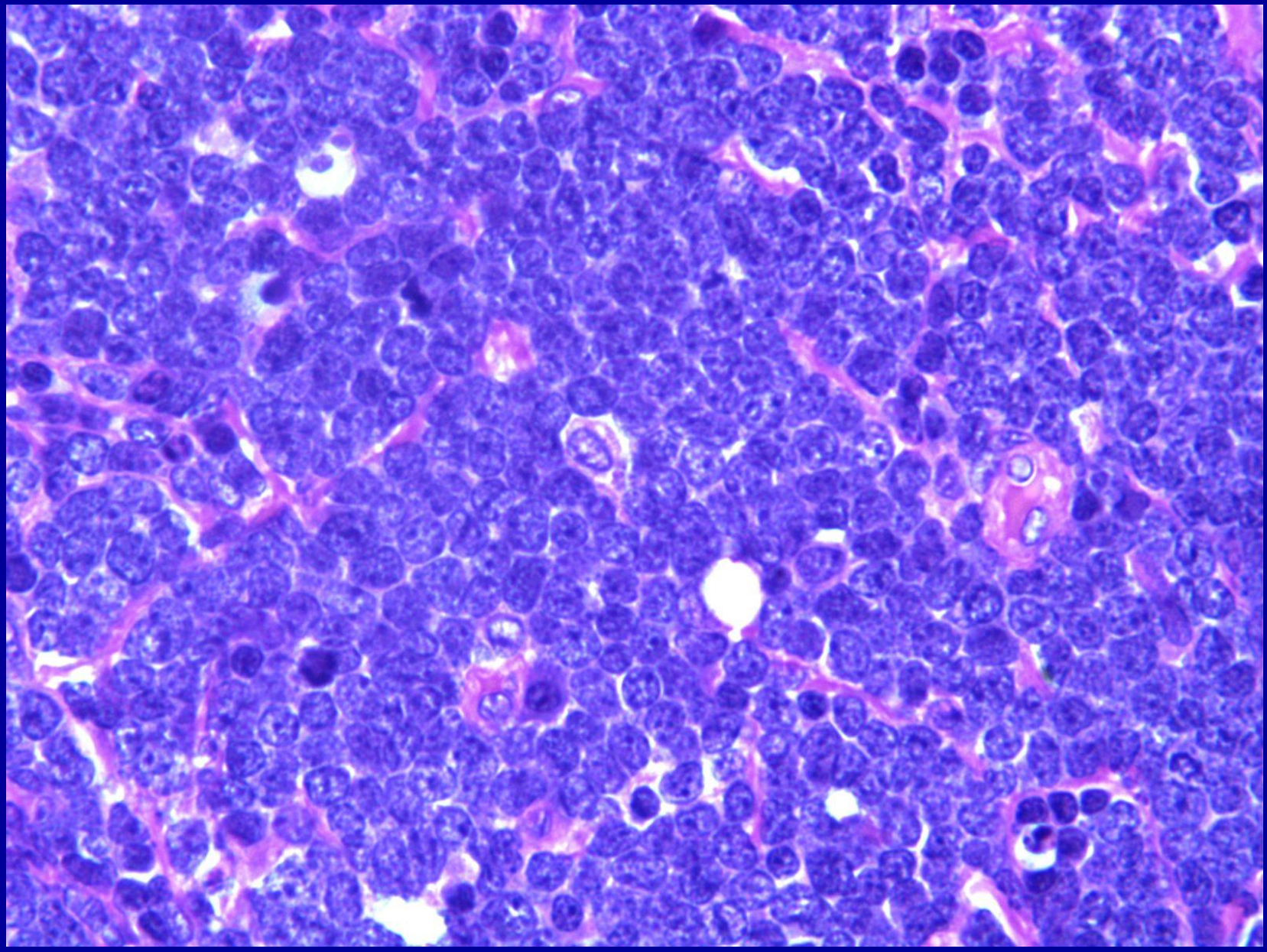
Histology	Gold standard*
Phenotype	Immunohistochemistry Flow cytometry
Genotype rearrangements	Antigen-receptor gene
	Chromosomal translocations
[t(14;18)]	
	Oncogenes (Bcl-1; Bcl-2)

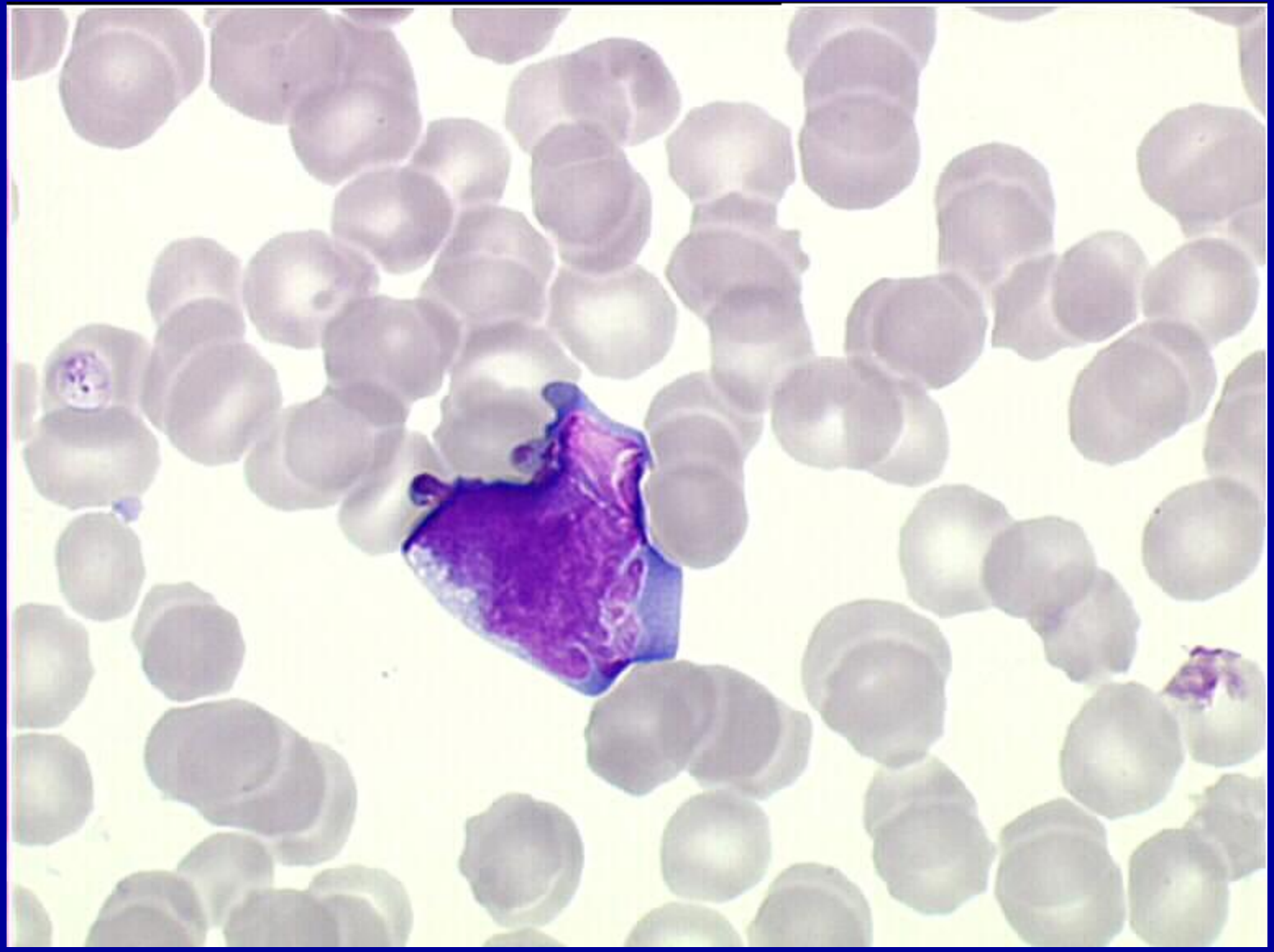
Precursor
B Lymphoblastic Lymphoma/Leukemia



- Very Aggressive
- B cell neoplasm
  - common in children
  - leukemic or lymphomatous phase
  - precursor B: CD19, CD10, tDt, HLADR
    - <1 % of all NHLs







Mature B-cell Malignancies (WHO)

- B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
- B-cell prolymphocytic leukemia
- lymphoplasmacytic lymphoma/Waldenstrom's M
- Splenic marginal zone B-cell lymphoma
- Hairy cell leukemia
- Plasma cell neoplasm
    - Multiple myeloma)
    - Plasmacytomas

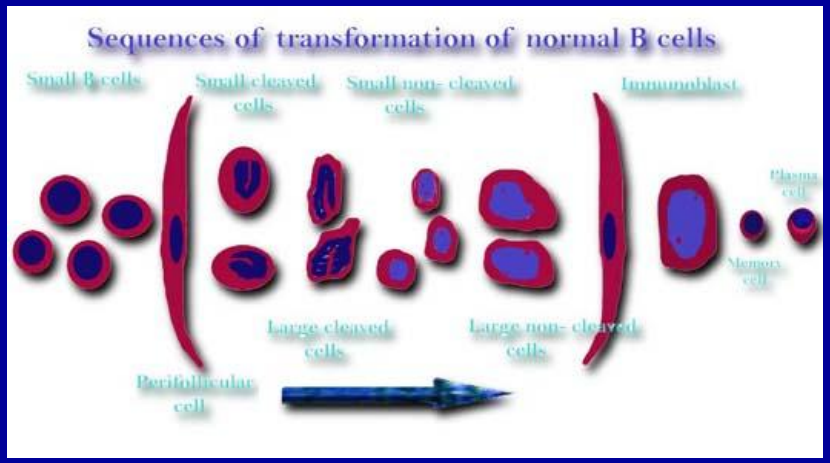
Extranodal Marginal Zone Lymphoma (MALT)

- Nodal marginal zone lymphoma
- Follicular lymphoma

Mantle cell lymphoma

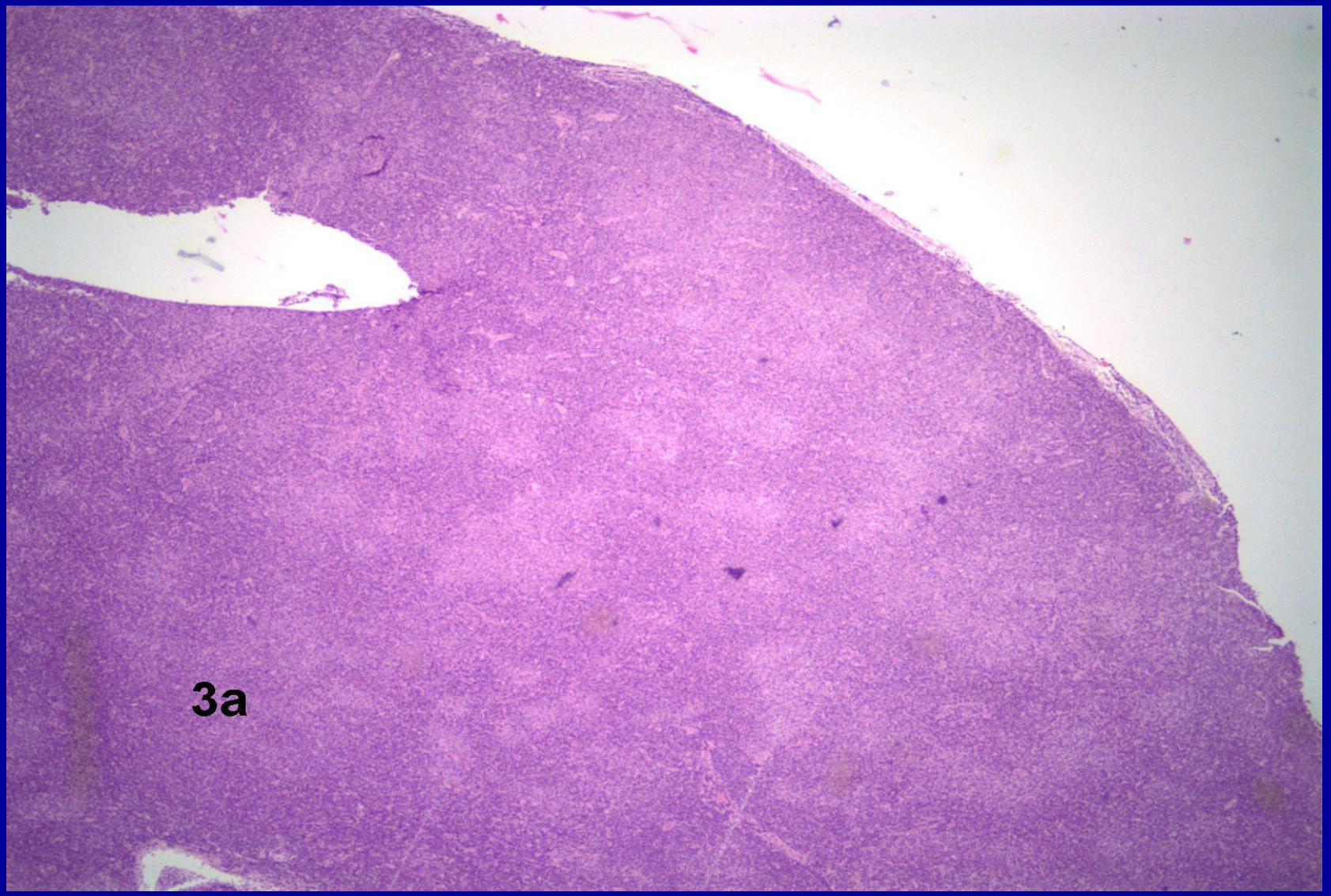
- Diffuse large B-cell lymphoma and variants
- Burkitt lymphoma

B cell small lymphocytic/CLL

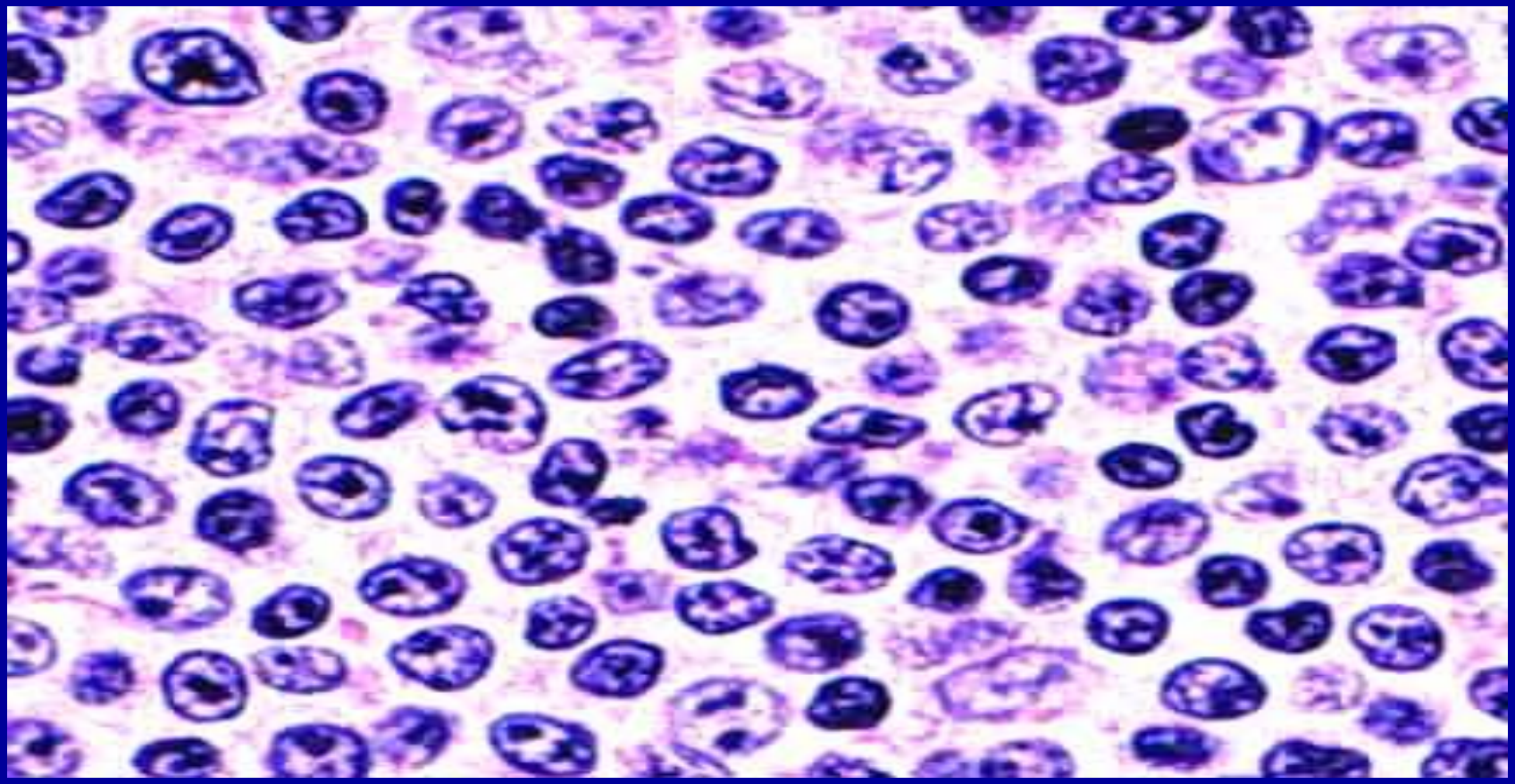


- 60 yrs median, 6.7 % incidence
- Indolent ; usually leukemic into bone marrow and spleen; may not require treatment
- small B-lymphoid cells clumped-nuclear chromatin
- B-cell (CD20, CD5,CD23, monoclonal light chain)
- Deletion 13q in 50 %
- Trisomy 12 in 20 %
- Richter's transformation-high grade lymphoma

CLL- Pseudofollicular “pale” areas



Prolymphocytes and paraimmunoblasts



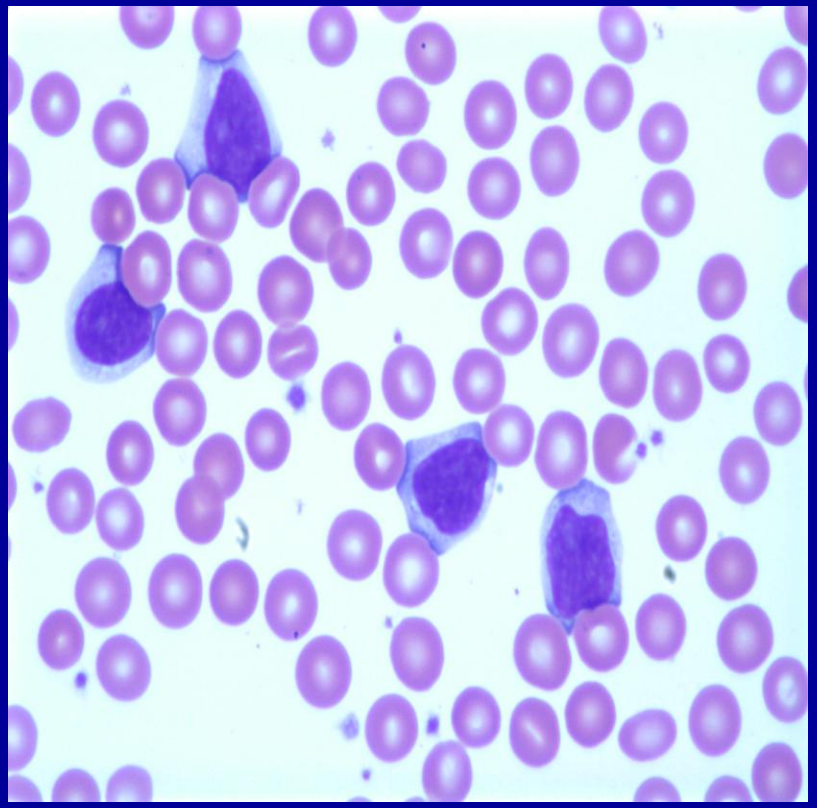
B-cell Prolymphocytic Leukemia

- Medium sized cytology prominent nucleoli
- Prolymphocytes =>55% of lymphs
- Clinical:
- <1% of all lymphocytic leukemias
  - 70 years old male
  - Marked splenomegaly, involvement of BM, PB
  - >100K lymphs
  - Poor survival

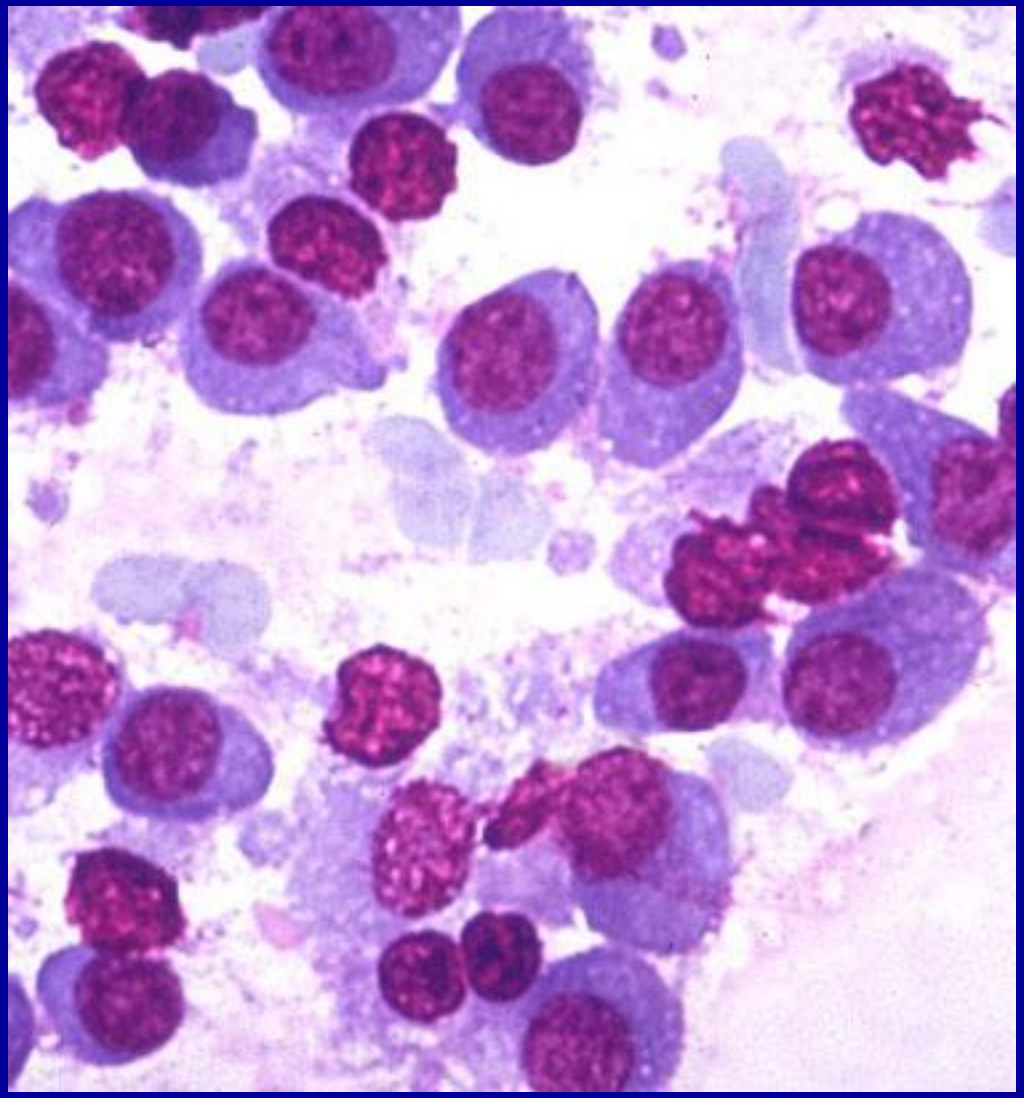
DDX and Immunophenotype

- DDX MCL blastic
  - CLL/PLL 11-55%
  - SMZL- no prolymphocytes

  -Immunophenotype
    - CD5 neg in 2/3 of cases
    - CD20+
    - CD23 negative
    - FMC7+
    - Strong SIg's

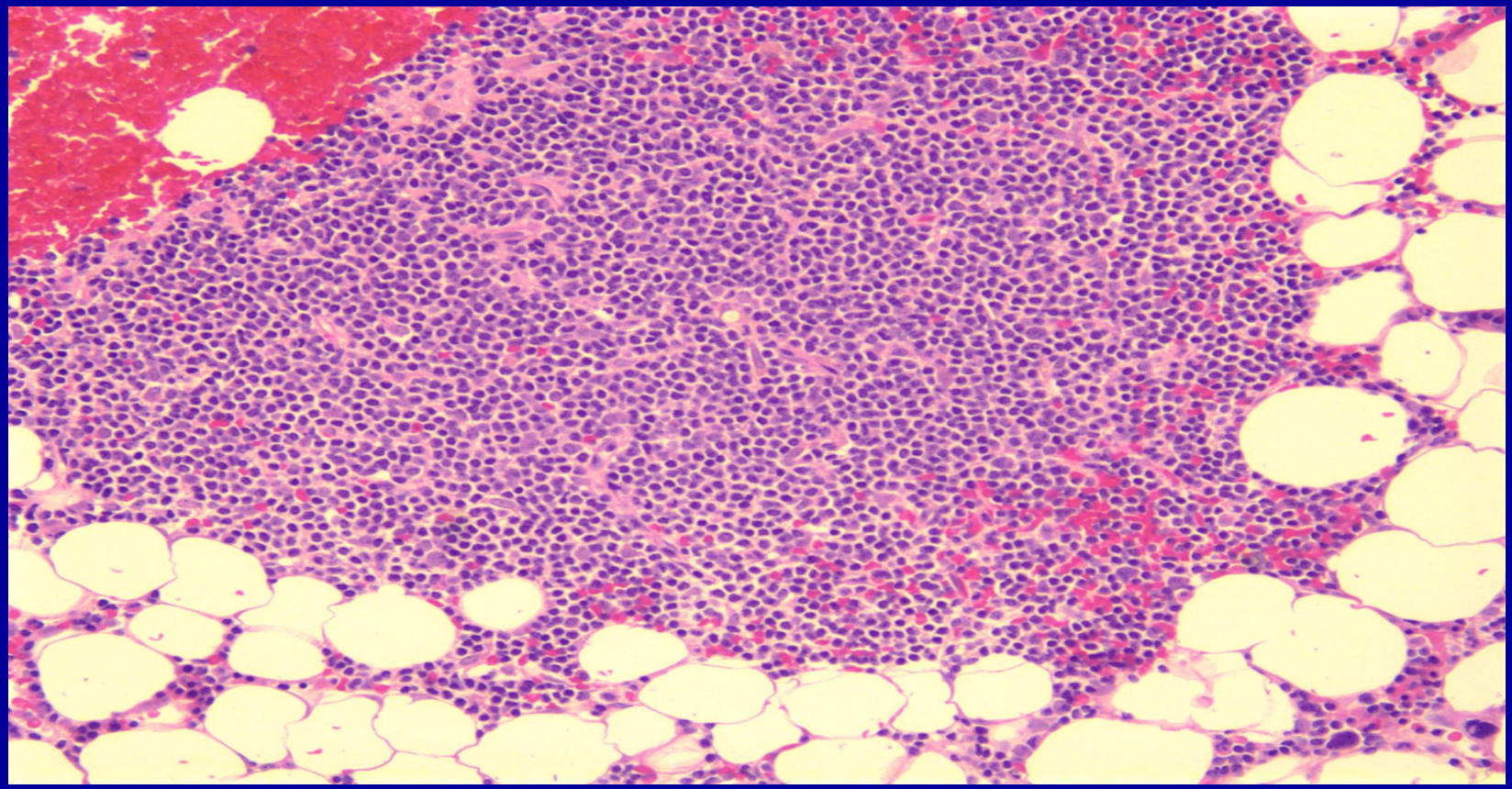


Lymphoplasmacytic Lymphoma

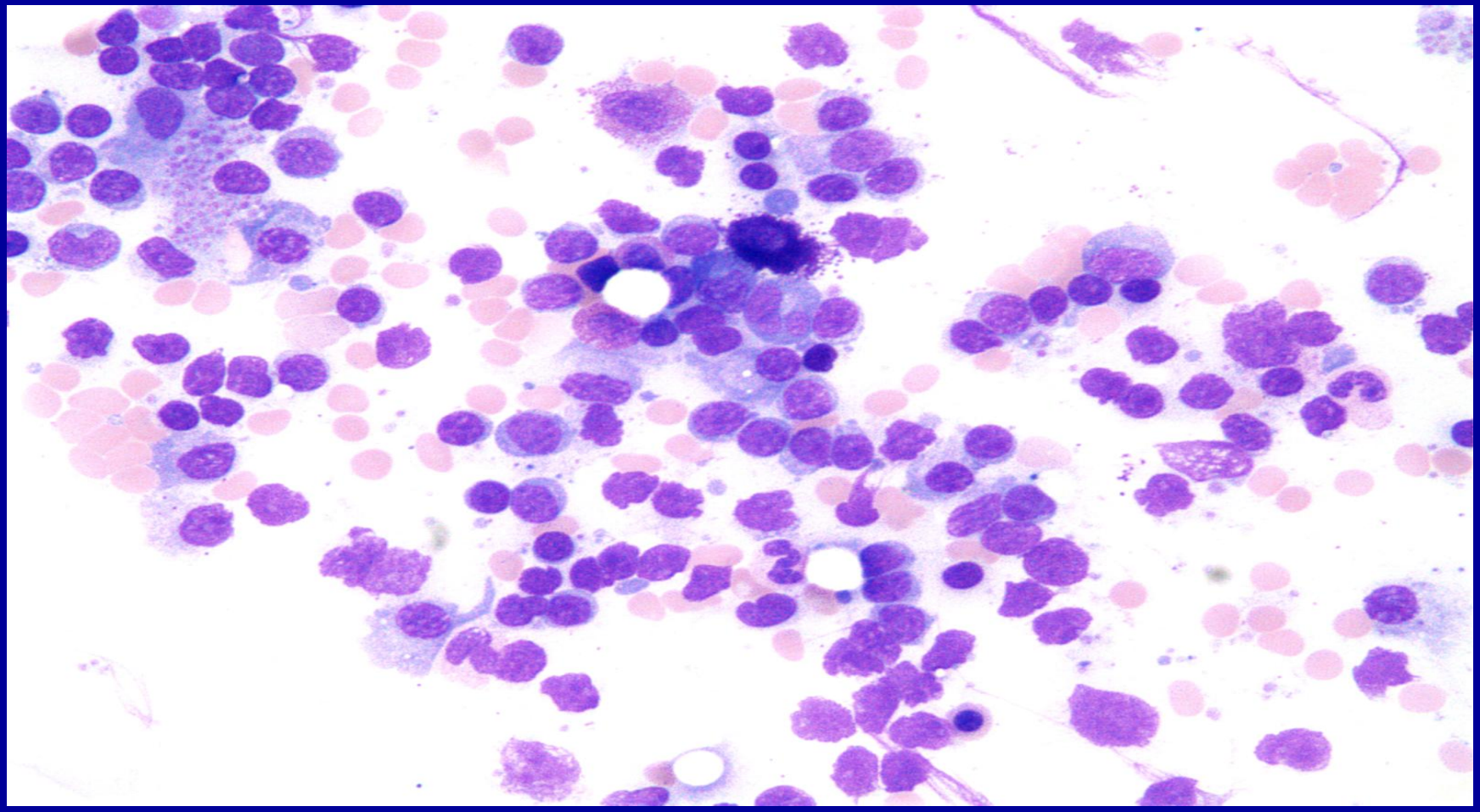


- 1.2 % WHO incidence
- Older patients with high serum viscosity and tumor in lymph nodes and bone marrow- Cytoplasmic and surface Immunoglobulin are monoclonal
- May involve focally
- Dutcher bodies
- T 9;14 in 50 %

Marrow diffuse or nodular pattern by Plasmacytoid lymphocytes



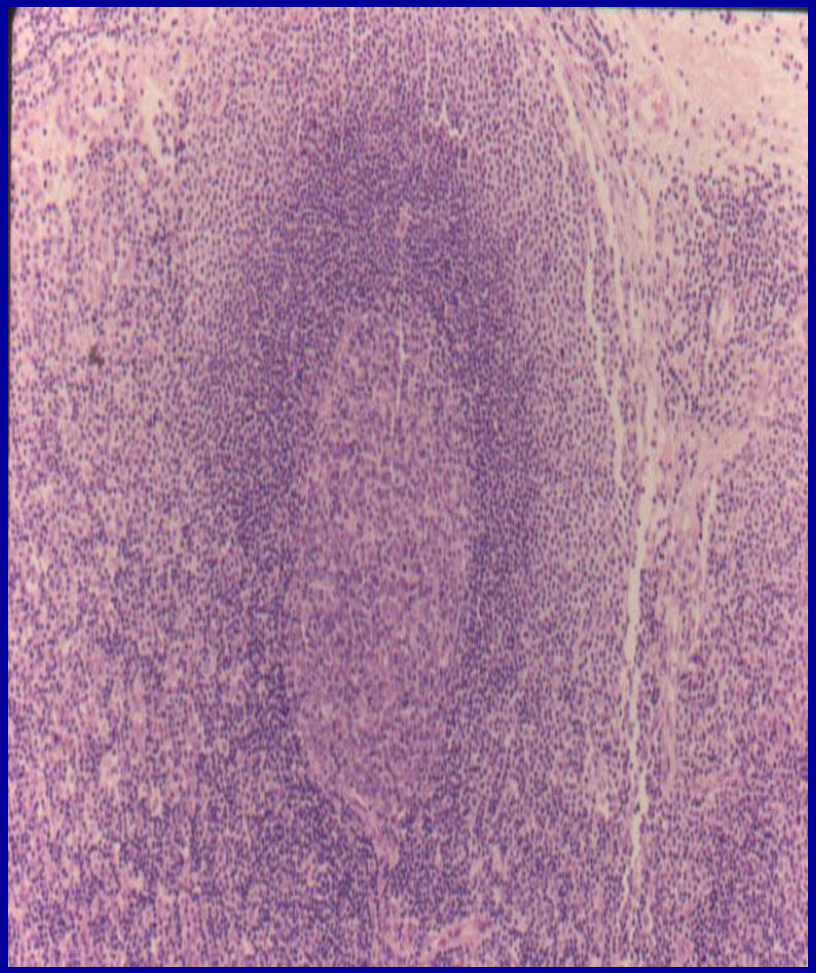
“Plymps”- lymphocytes, lymphoplasmacytes, plasma cells



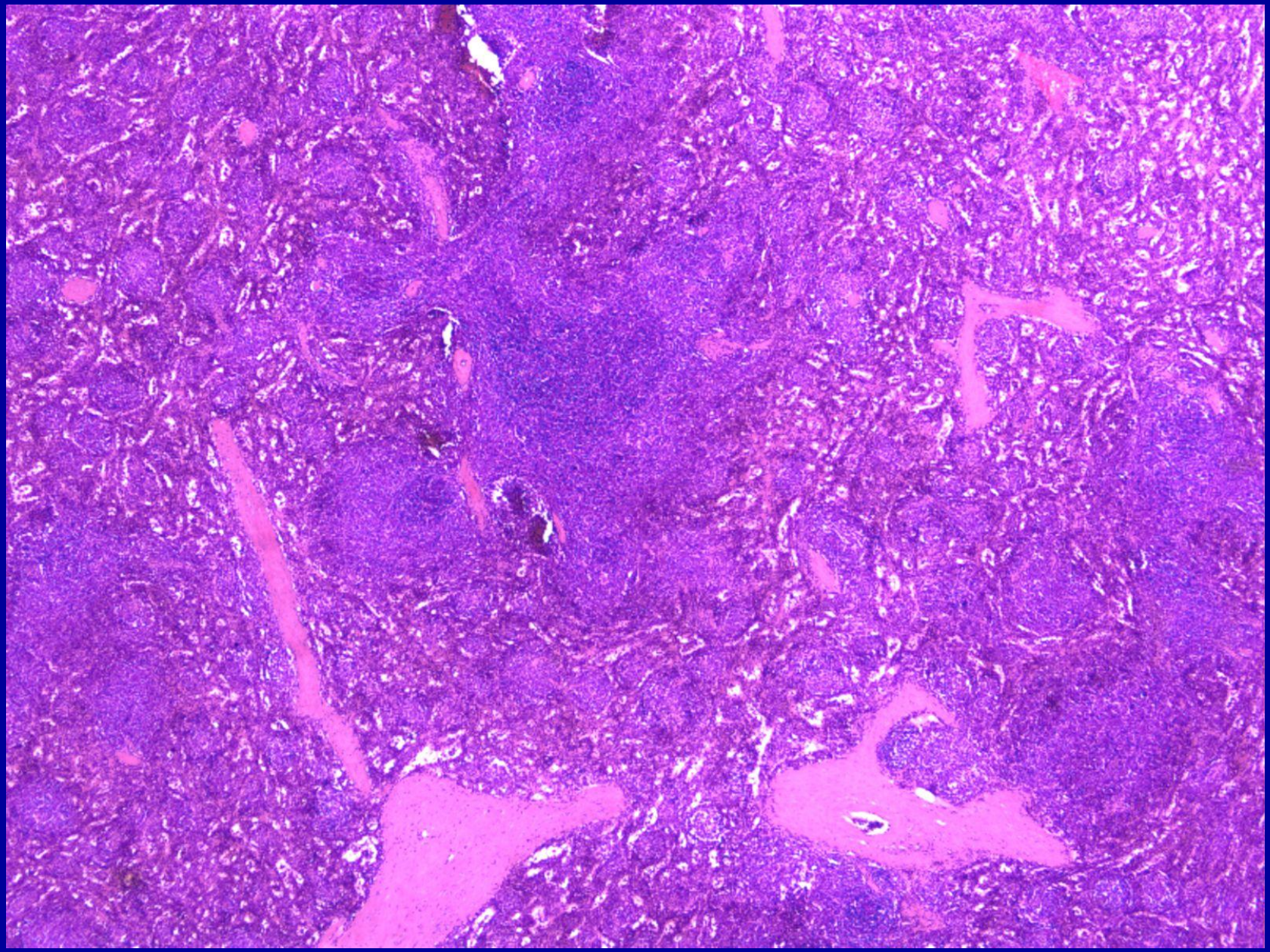
Waldenstrom's Macroglobulinemia

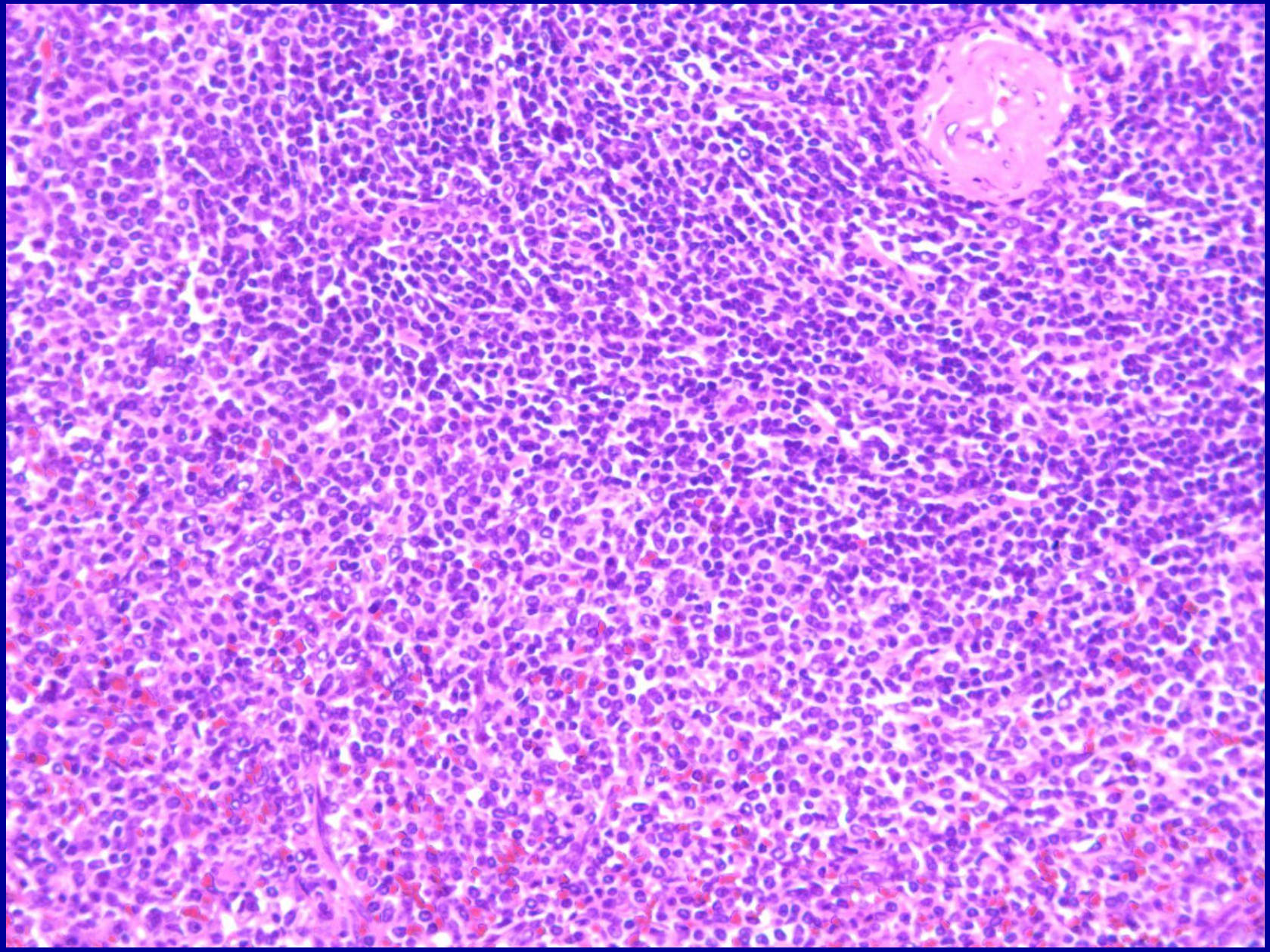
- 10-15 % of all monoclonal gammopathies
- chronic lymphoproliferative disorder
- median age 72
- IgM paraprotein
- Hyperviscosity is common
- plasma cells and lymphocytes and plasmacytoid lymphocytes

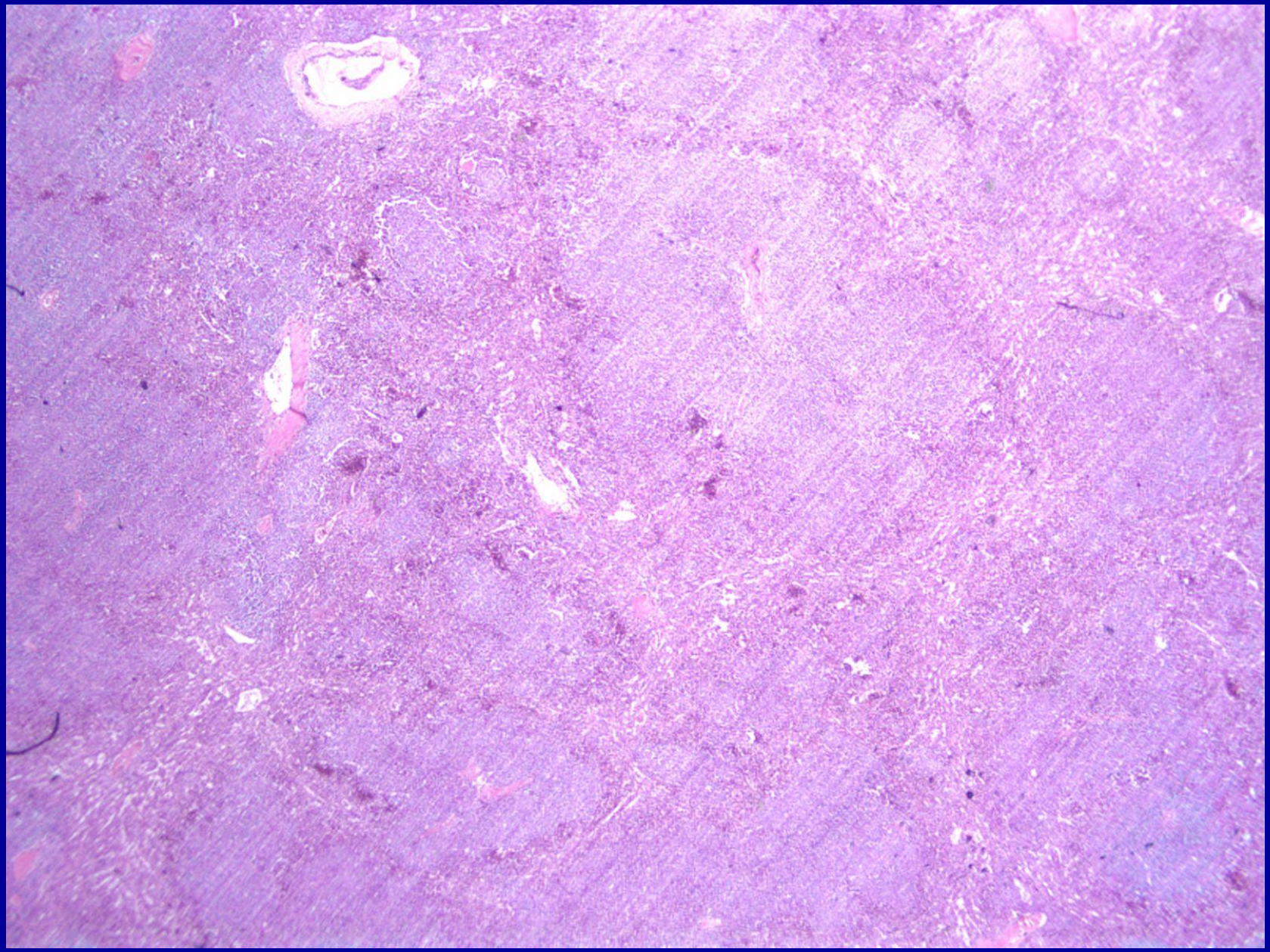
Splenic Marginal Zone Lymphoma

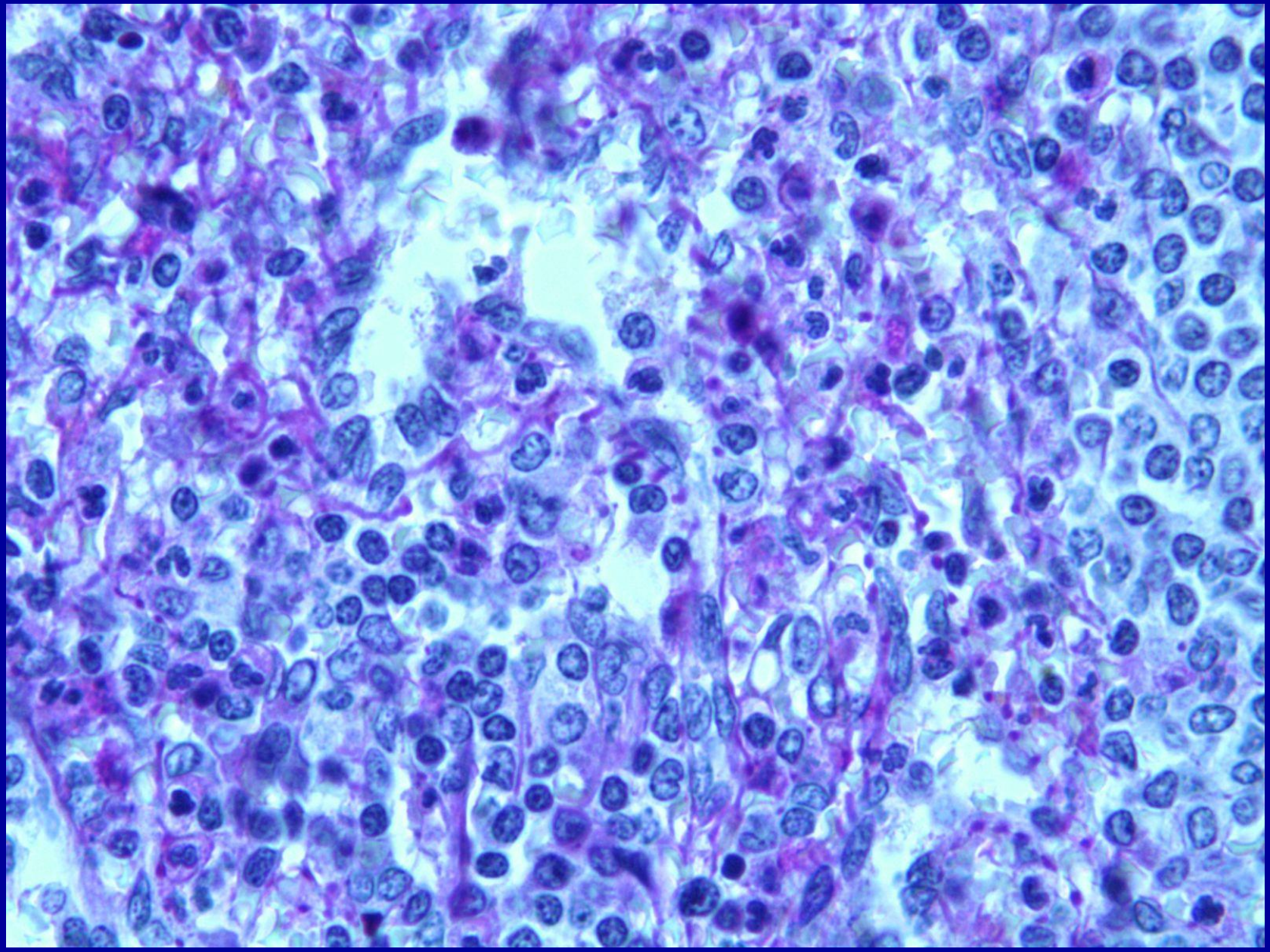


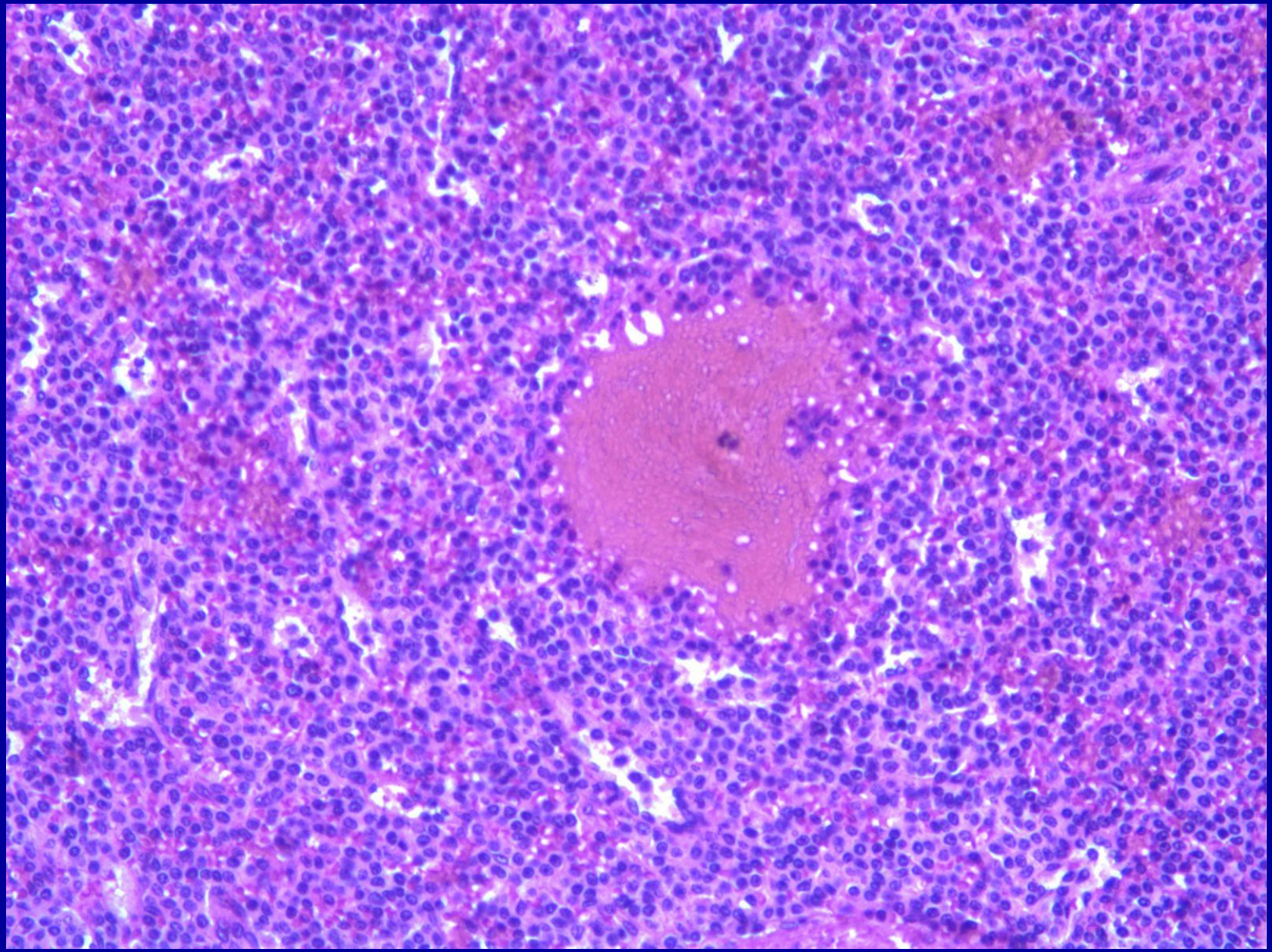
- Rare <1 % of lymphoid neoplasm
- BM, Blood, Spleen
- Splenomegaly with AIHA, paraprotein
- Tripartite or bipartie white pulp
- CD5- CD10- light chain restricted
- CD11c+, CD25- , TRAP negative
- Indolent, may transform
- Hepatitis C associated

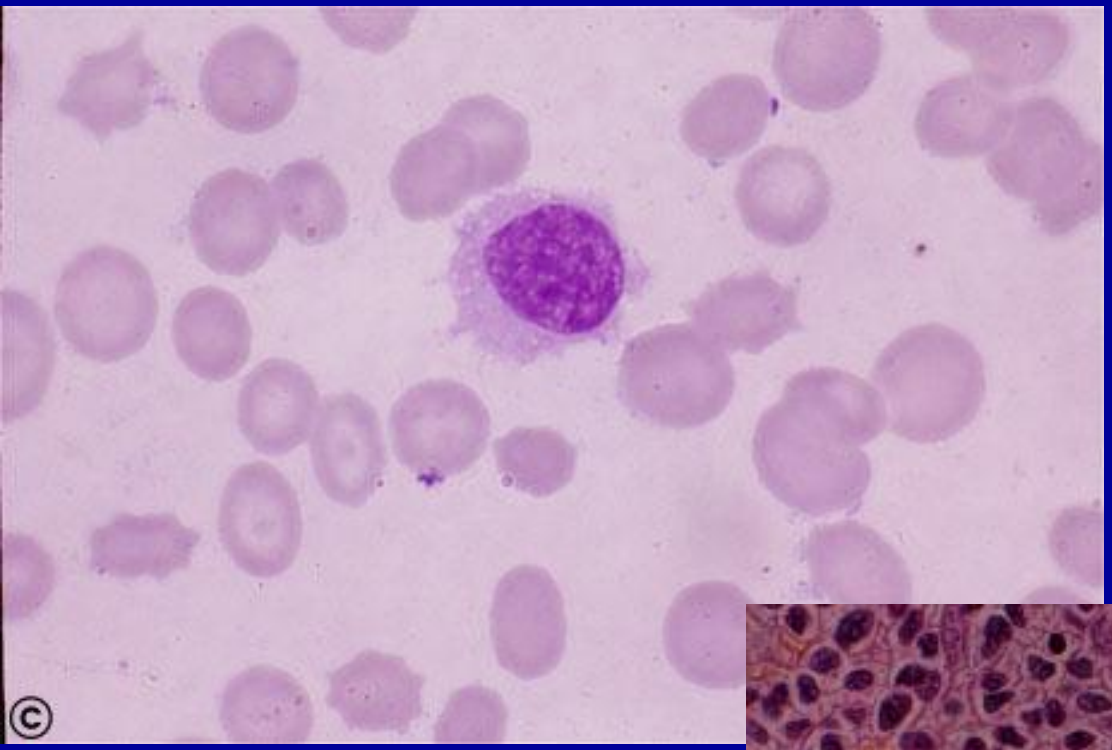


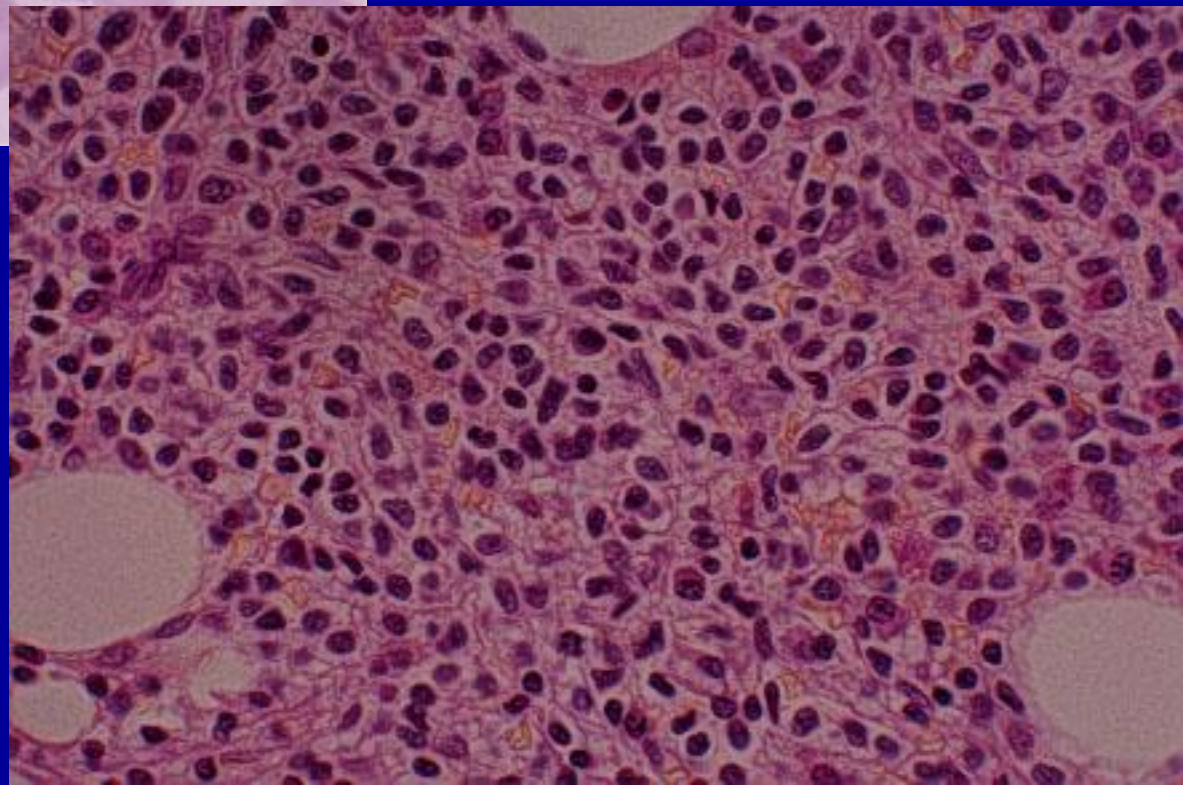




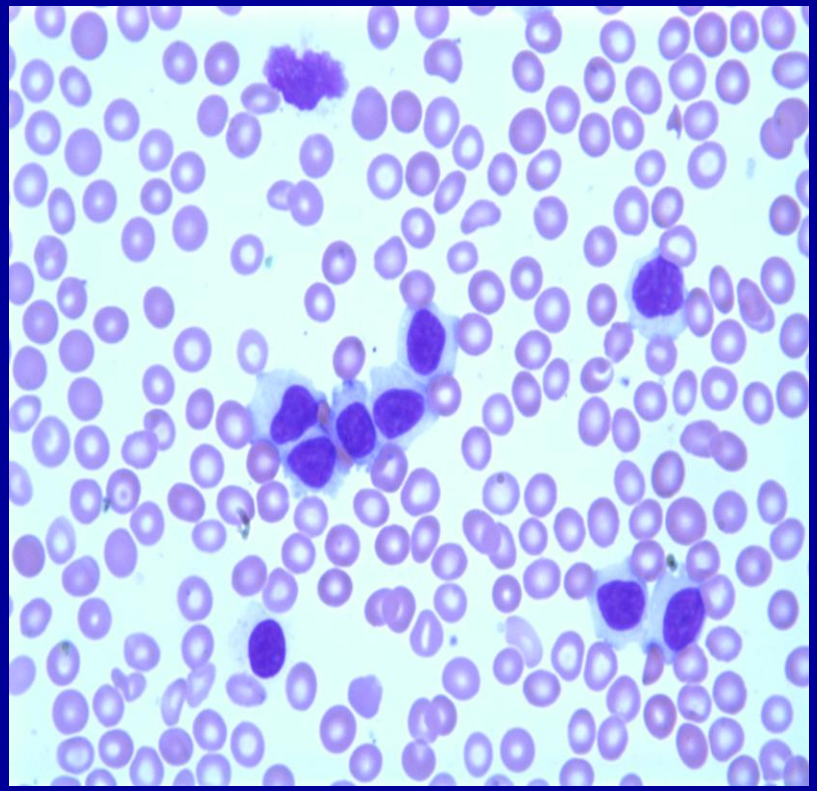






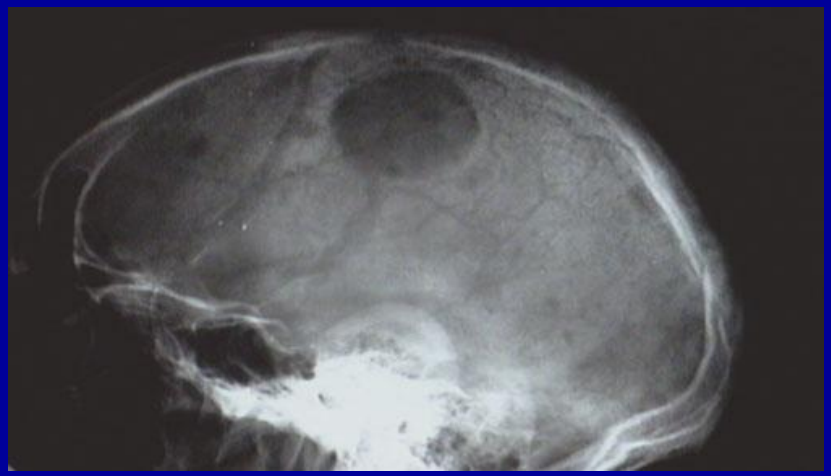


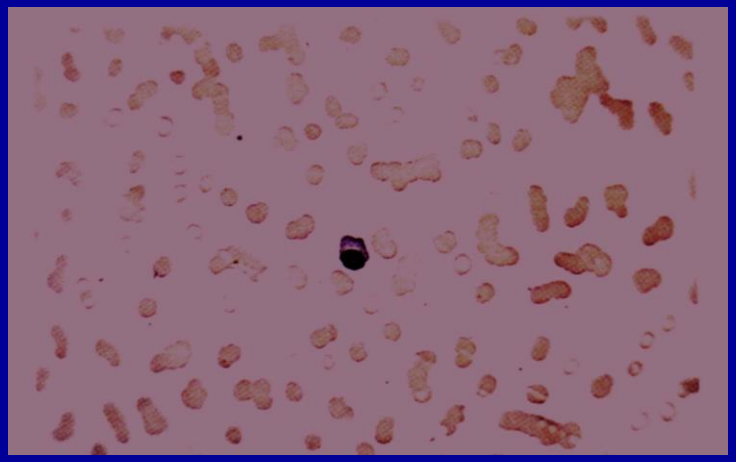
Hairy Cell Leukemia- PBS and Immunophenotype

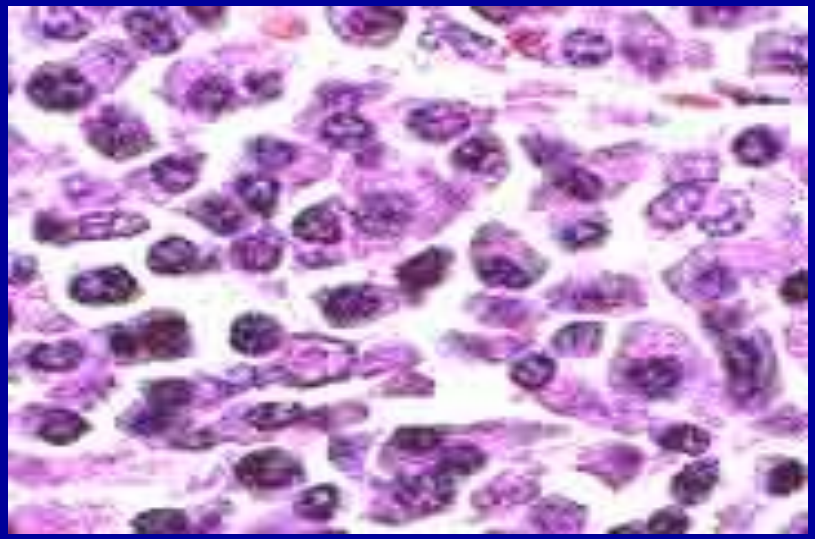


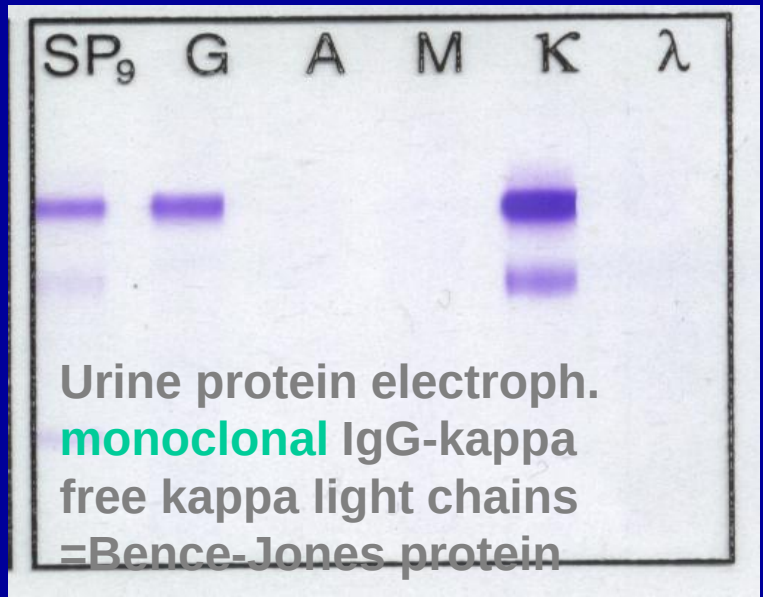
- CD103+
- CD20+
- CD11c+
- CD25+
- Trap- Tartrate resistant acid Phosphatase

Myeloma







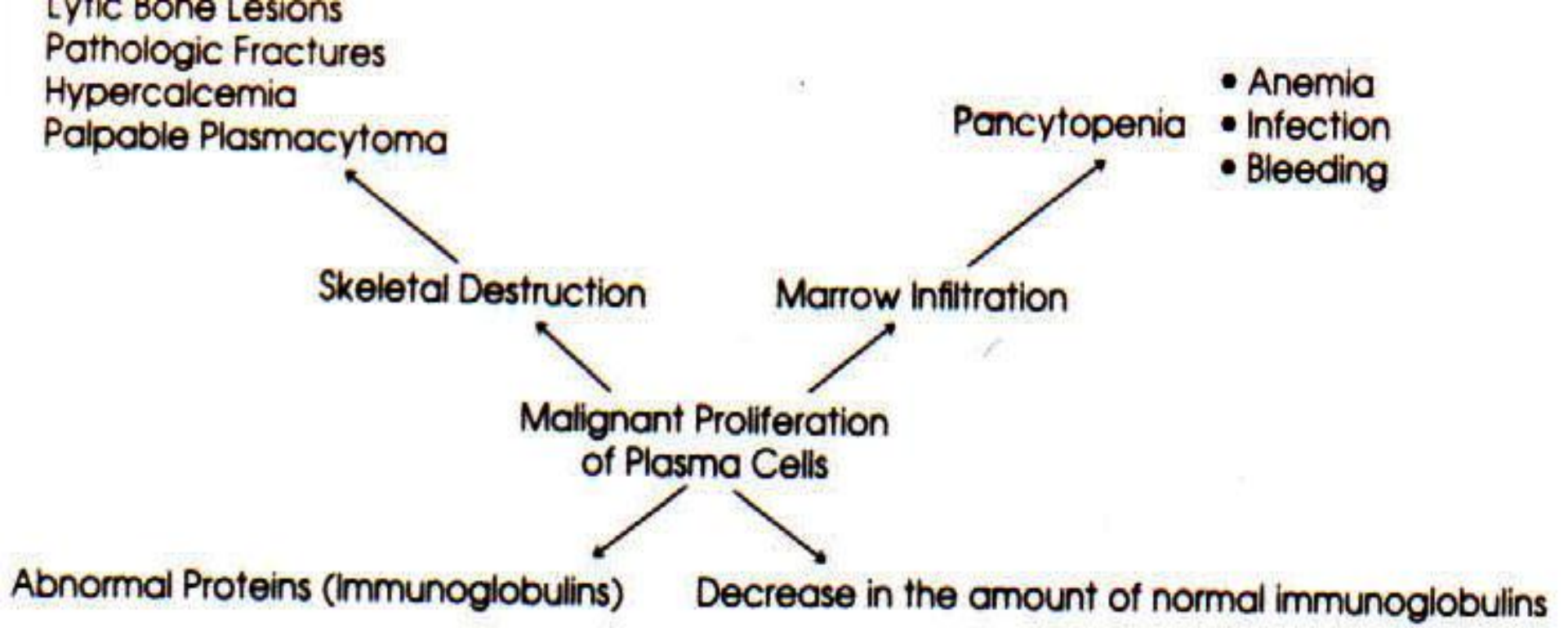

SP9 G A M κ λ
Urine protein electroph.
monoclonal IgG-kappa
free kappa light chains
=Bence-Jones protein

MULTIPLE MYELOMA (MM)

1-2 % of all cancers,
10-15% of all lymphohematopoietic malignancies
median age 71
3:2 M>F
Black >White
3.6 cases per 100,000 population

Multiple Myeloma Triad

- **monoclonal paraprotein in serum or urine**
- **bone changes leading to pain and pathologic findings**
- **excess plasma cells in the bone marrow**



Urinary:
- Bence-Jones Proteinuria
- Myeloma Kidney

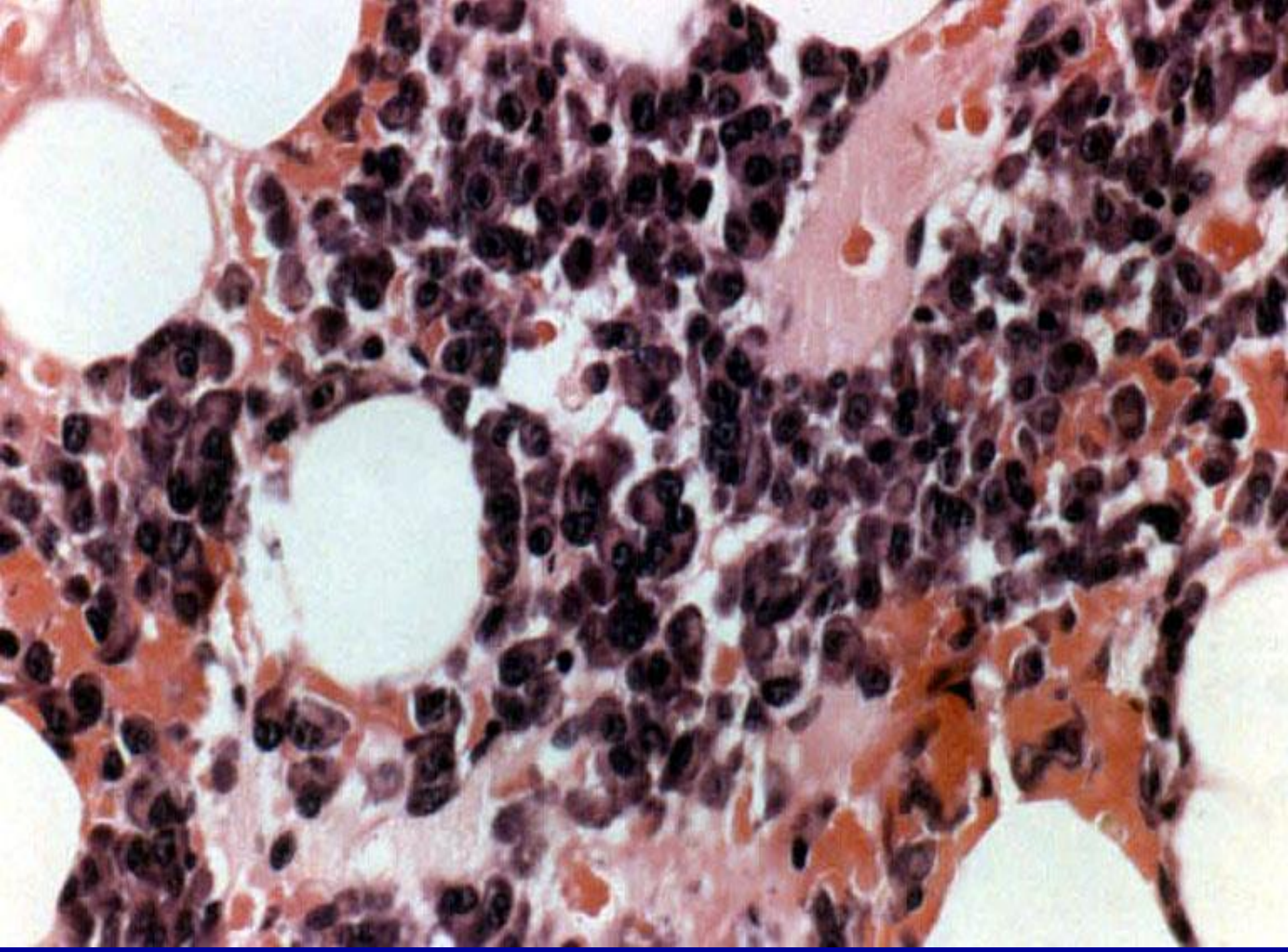
Blood:
- Cryoglobulin
- Hyperviscosity
- Bleeding Disorders — Interference with Clotting Factors

Infection

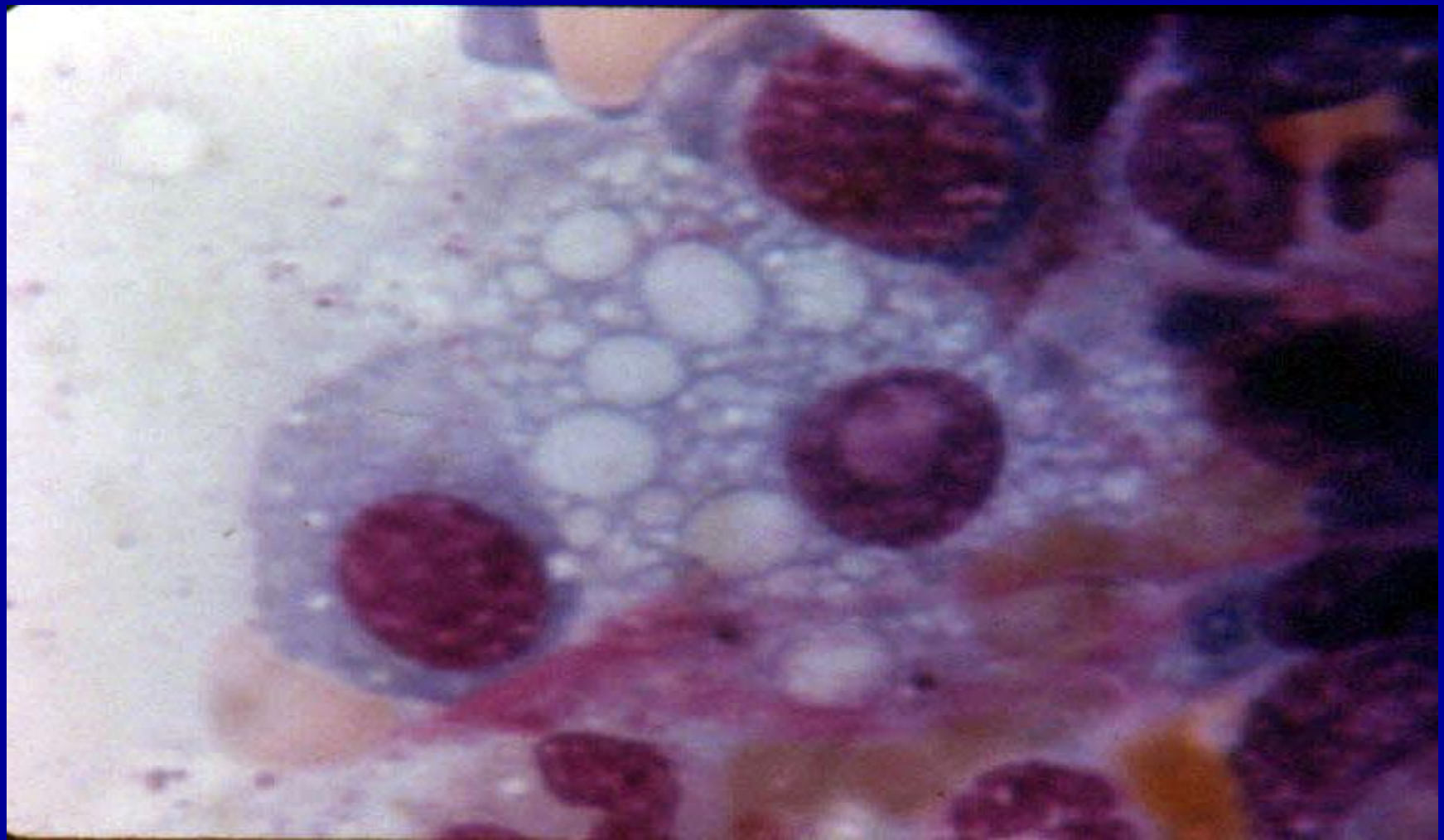
Tissues:
- Amyloidosis
- Organomegaly
- Loss of Function

Indications for serum protein electrophoresis

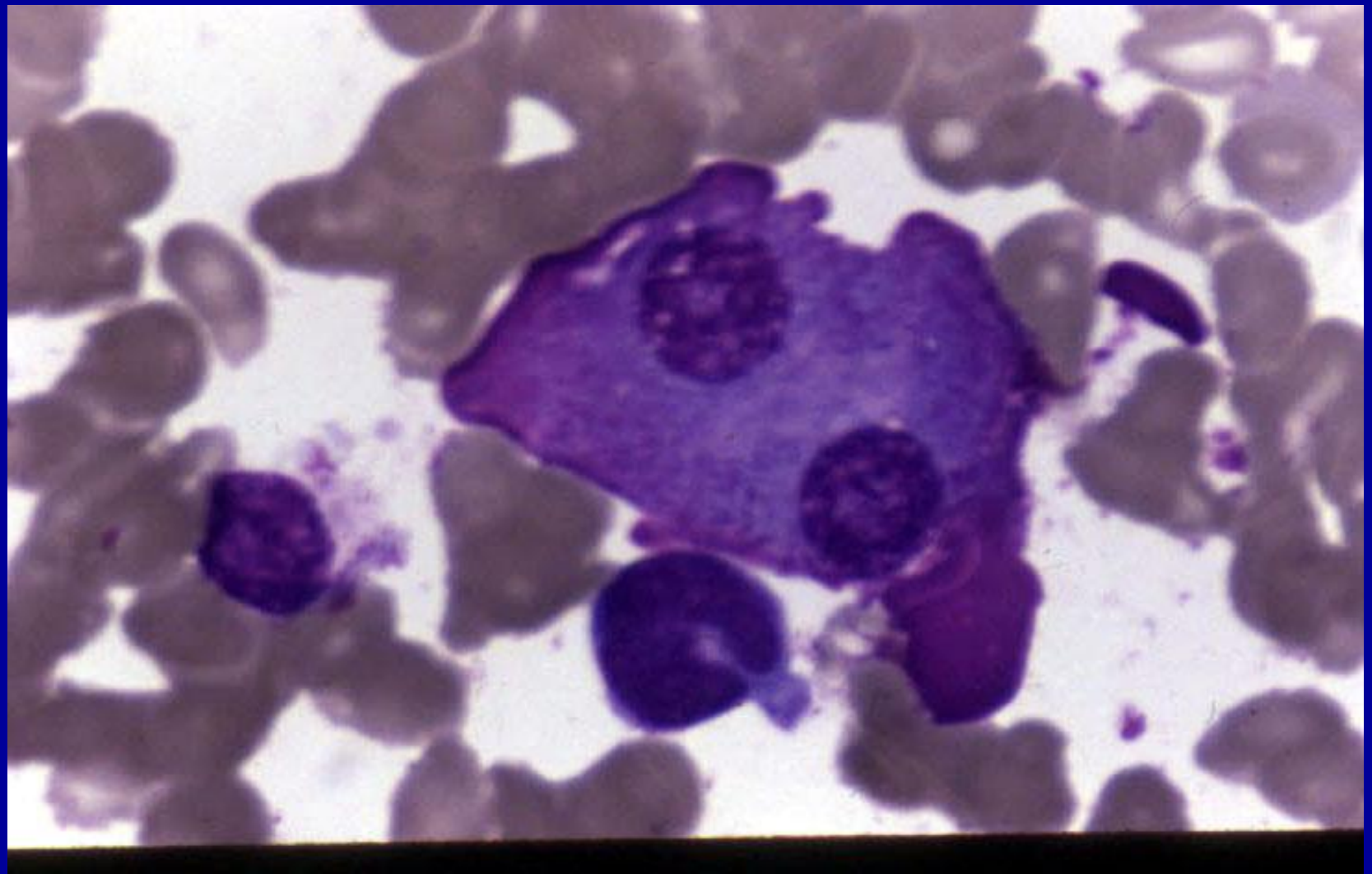
- **anemia**
- **unexplained back pain**
- **weakness or fatique**
- **osteolytic lesions or fractures**
- **osteopenia**
- **hypercalcemia**
- **renal insufficiency**
- **presence of Bence Jone proteinuria**
- **history of recurrent bacterial infections**
- **unexplained neuropathy or carpal tunnel syndrome,etc.**



Proplasma cells, Mature PC

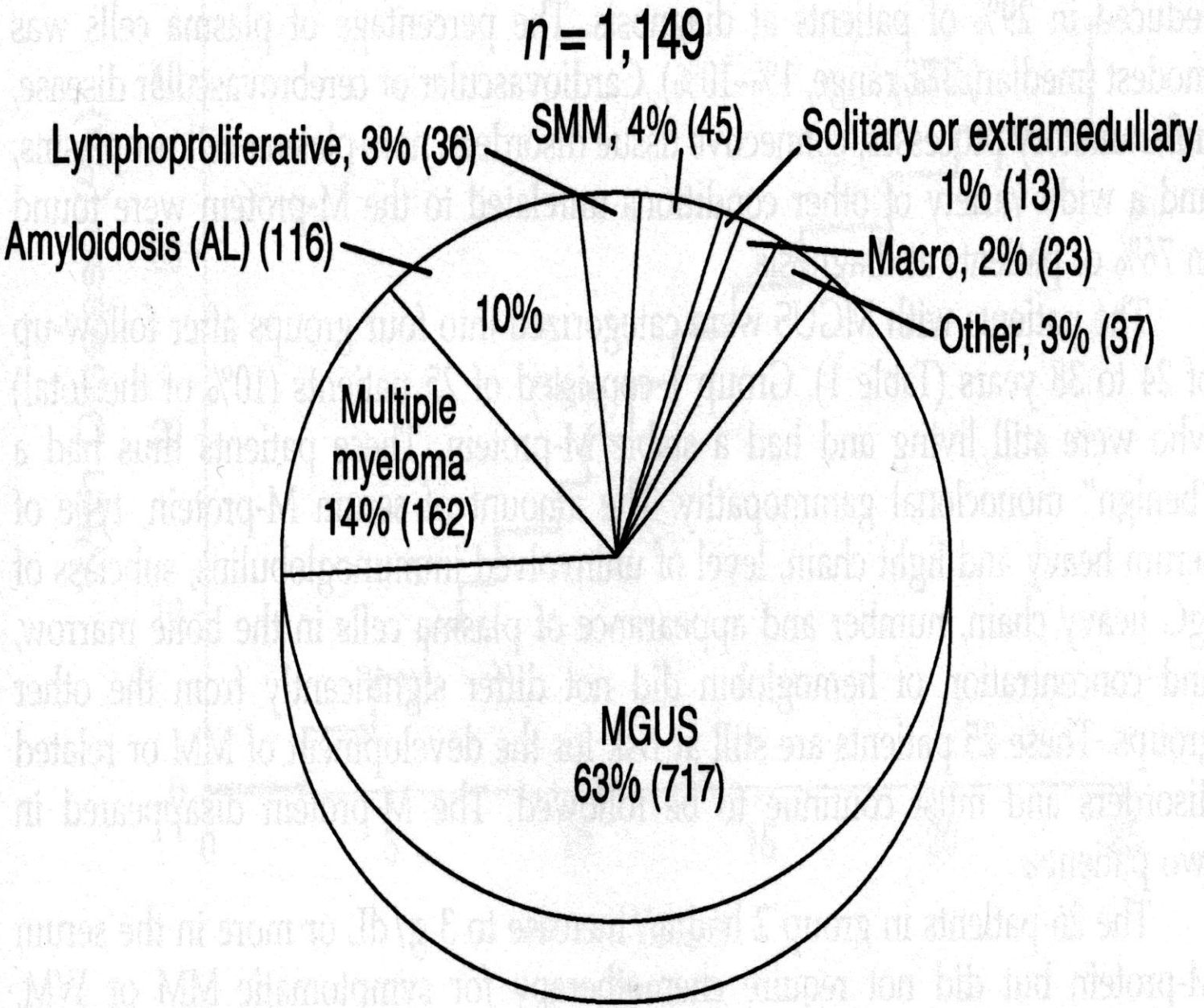


Flame cells- IgA



Monoclonal Gammopathy of undetermined significance (MGUS)

- also called **benign monoclonal gammopathy**
- **one percent of healthy people over the age of 50 and in three percent of people over the age of 70**
- **more common than myeloma**
- **low serum and stable paraprotein (<2 g/dl)**
- **no reduction in normal immunoglobulins**
- **absence of skeletal abnormalities**
- **less than 10 % plasma cells in marrow, no Bence Jones**
- **may progress to myeloma/ plasmacell dyscrasia in 10-40 % of patients over few decades**


n = 1,149
Lymphoproliferative, 3% (36)
SMM, 4% (45)
Solitary or extramedullary
1% (13)
Amyloidosis (AL) (116)
Macro, 2% (23)
10%
Other, 3% (37)
Multiple
myeloma
14% (162)
MGUS
63% (717)

MGUS Status After Average (n=241, 22 yrs ffup)

	Percent
No progression of M-component	19%
Developed malignant immunoproliferative disease;	24%
MM in	16%
Died of unrelated causes	47%
M-component became > 3 g/dl	10%

Follow up of patients:

recent diagnosis- ffup SPEP in 3 and 6 months, then yearly thereafter

annual SPEP if serum M-spike < 1.5 g/dL

Smoldering Myeloma

- **asymptomatic patients with M-component > 3 g/dL**
- **plasma cells >10 but less than 20 % in bone marrow**
- **no therapy until progression**
- **usually 5 years without change, then reclassify as MGUS**
- **Like indolent myeloma but latter has criteria like myeloma with no clinical progression**

Solitary plasmacytoma and Extramedullary plasmacytoma

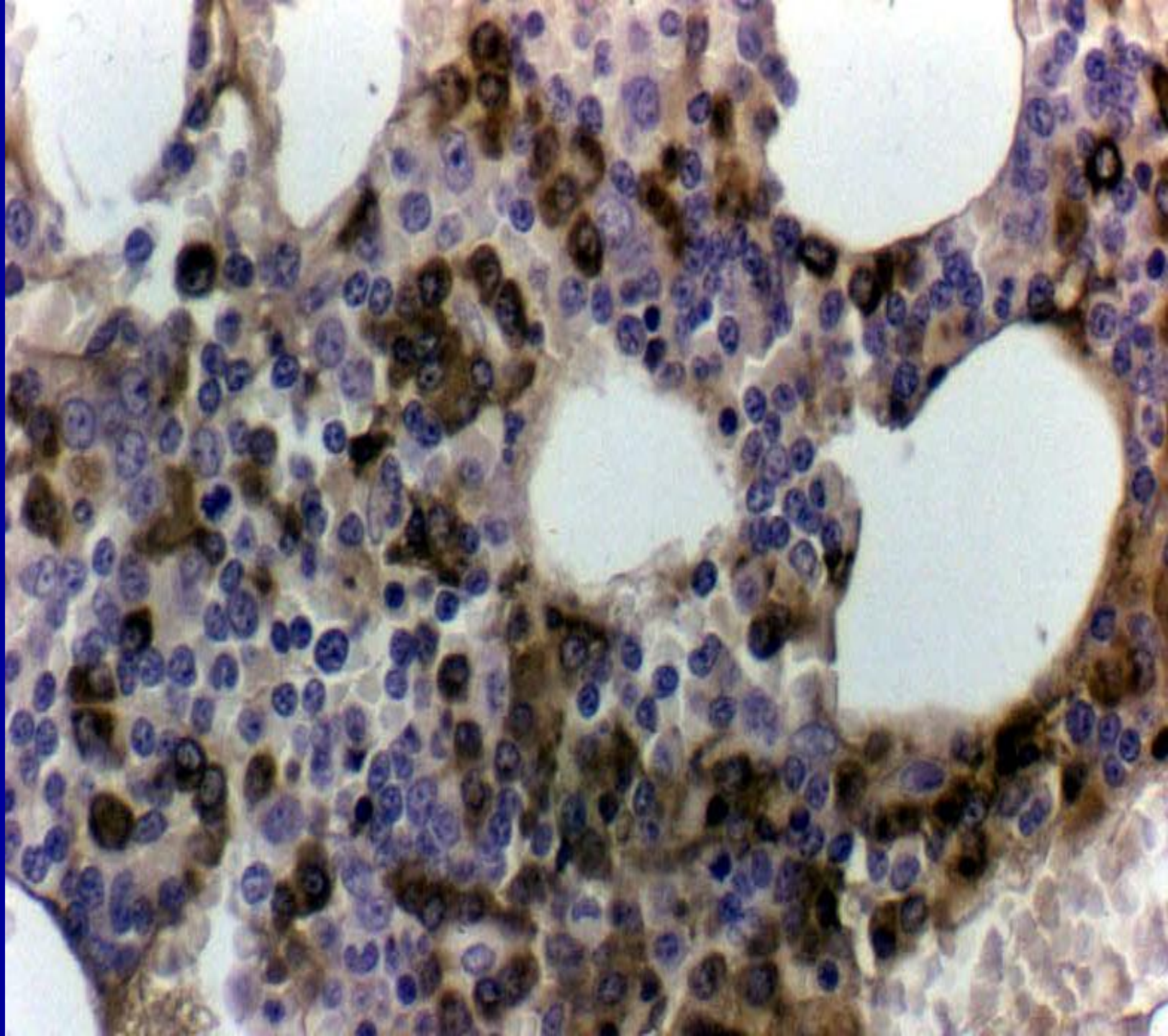
- Solitary plasmacytoma of bone
  - **56 mean age, male, spinal disease, M protein 1/3 to 2/3**
  - **2/3 eventually develop myeloma**
- ,extra-medullary plasmacytomas
  - common in head and neck-nasopharyngeal or paranasal sinuses
  - have an excellent prognosis: after excision and local radiotherapy, most of them are cured.
  - Prognosis good

Light chain myeloma

- **Bence Jones protein only or free light chains disease**
- **renal failure common**
- **10-15 % of all monoclonal gammopathies**
- **despite low levels of paraprotein, significant clinical problems are seen especially pathologic renal diseases-due to toxicity of light chains in tubules**

Non-secretory Myeloma

- **absent detectable M-protein in both serum and urine**
- **1-5% of all multiple myeloma**
- **Immunohistochemistry detects cytoplasmic M-protein in 85 %**
- **In 15 % of NS, true non-secretory**
- **median survival 39-45 months**



Plasma cell leukemia

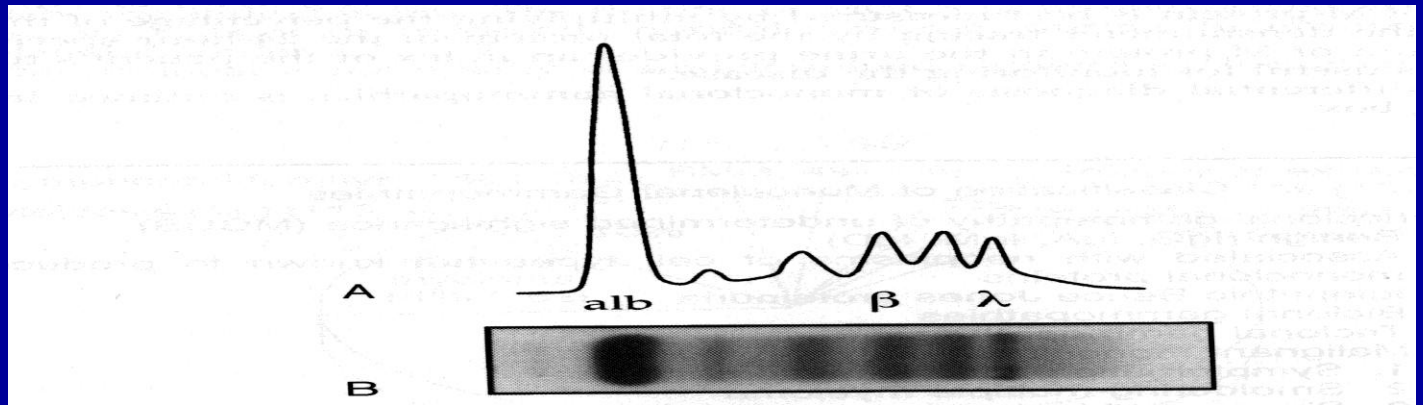
- 2-4 % of all immunoproliferative diseases
- de novo or with hx of MM
- aggressive disorder in which a large number of plasma cells circulate
- >20 % plasma cells in blood
- prognosis is poor

Heavy chain diseases

- **Franklin reported the first case- Gamma heavy chain**
- **IgA heavy chain or Mediterranean lymphoma most common**
- **Mu chain disease rare**
- **since these are rare, a heavy chain only reaction may require dilution to show light chain obscured by antigen excess**
- May present like CLL

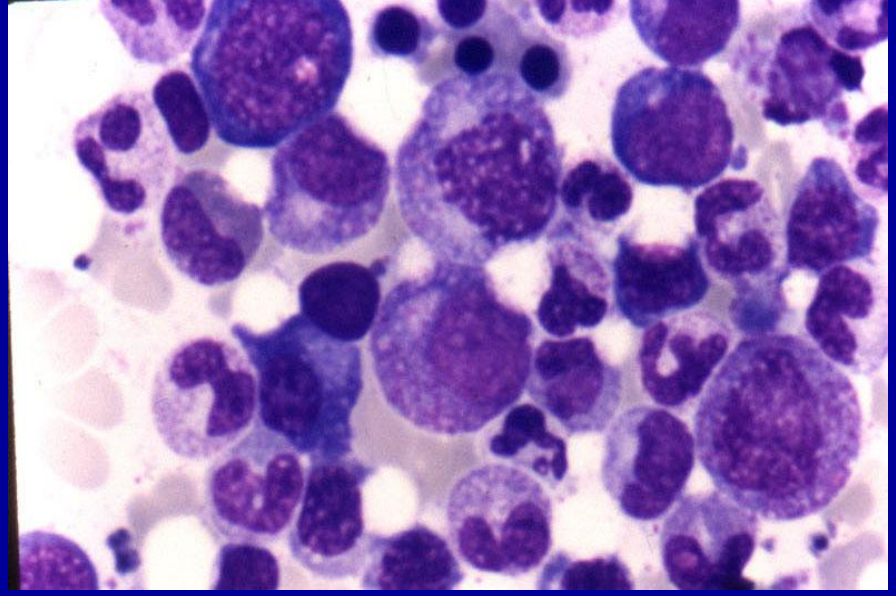
Biclonal gammopathies

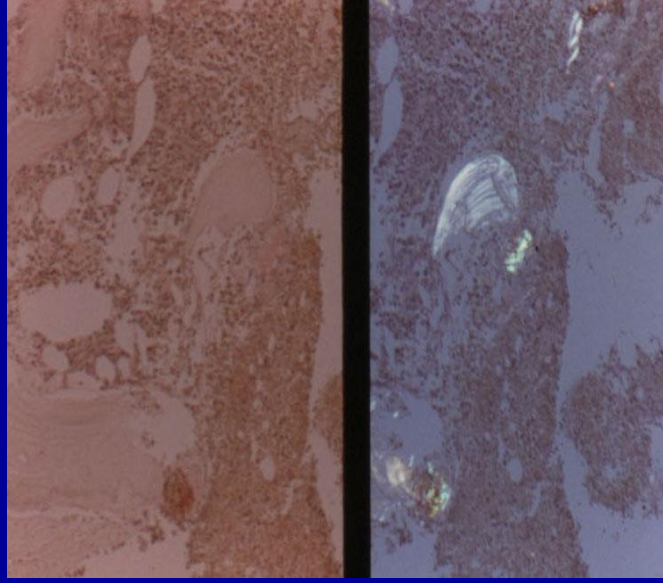
- very rare, 3-4 %
- MGUS in 65 %,
- Lymphoma in 19 %,
- MM in 16 %-same as monoclonal MM in prognosis
- rule out dimerization or breakdown of units of IgM or IgA
- - most frequently detected by Immunofixation

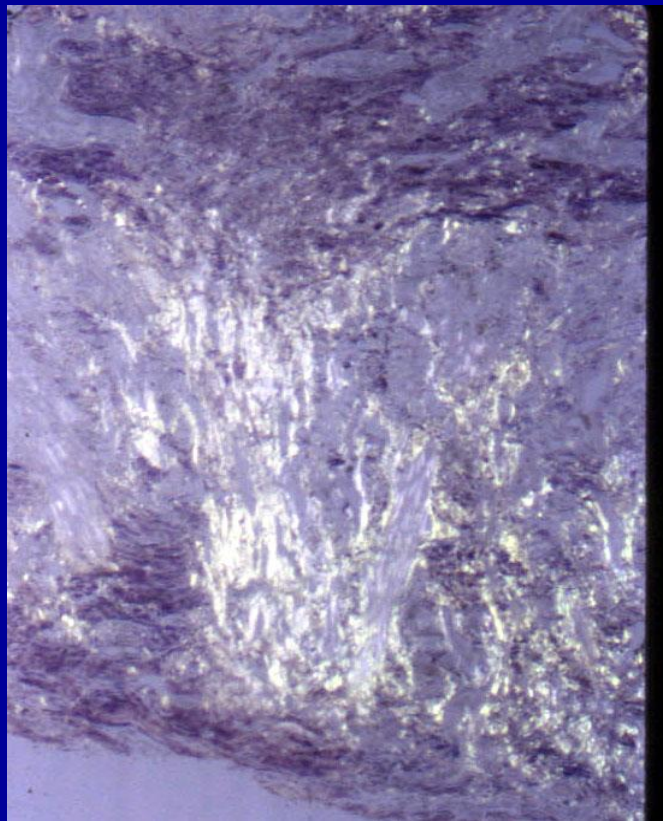


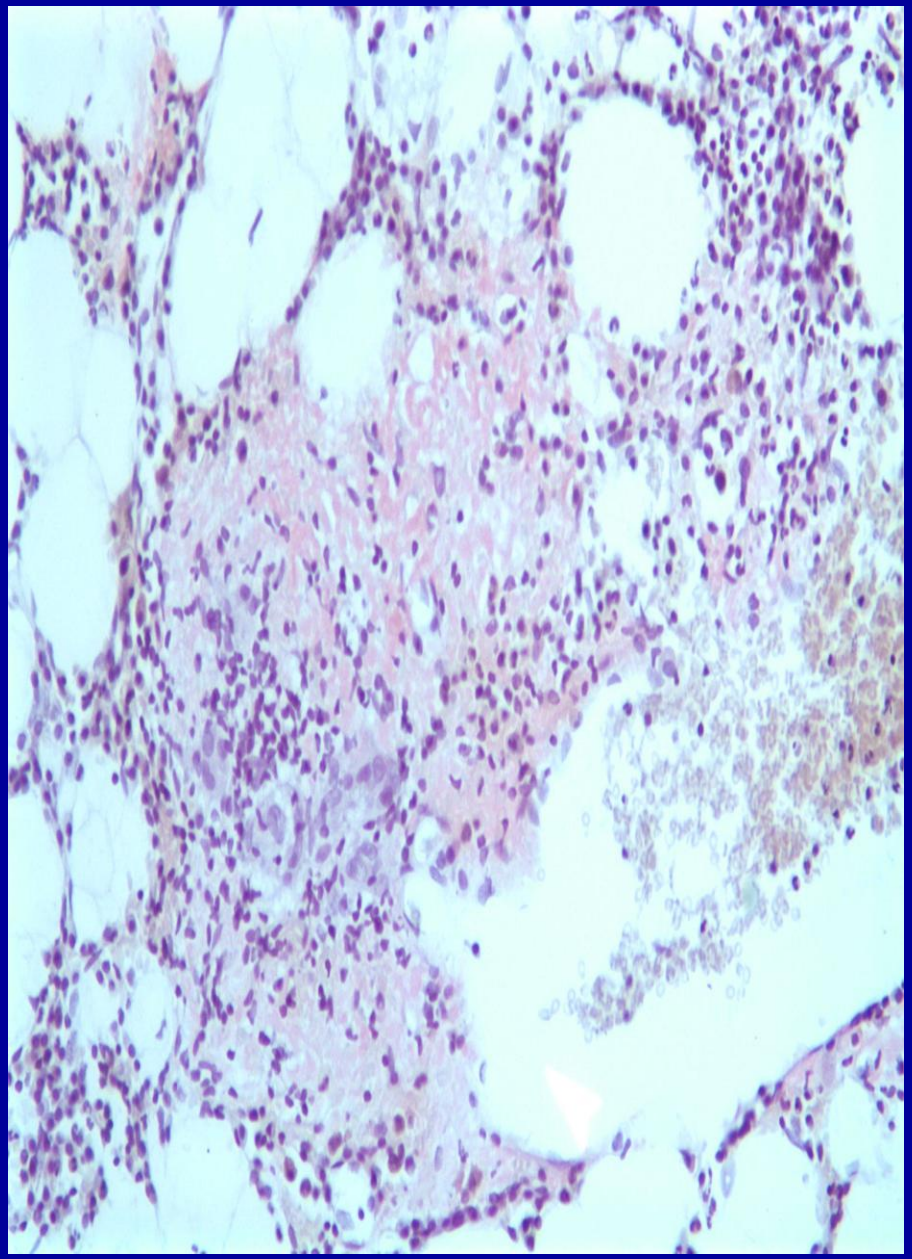
Primary amyloidosis

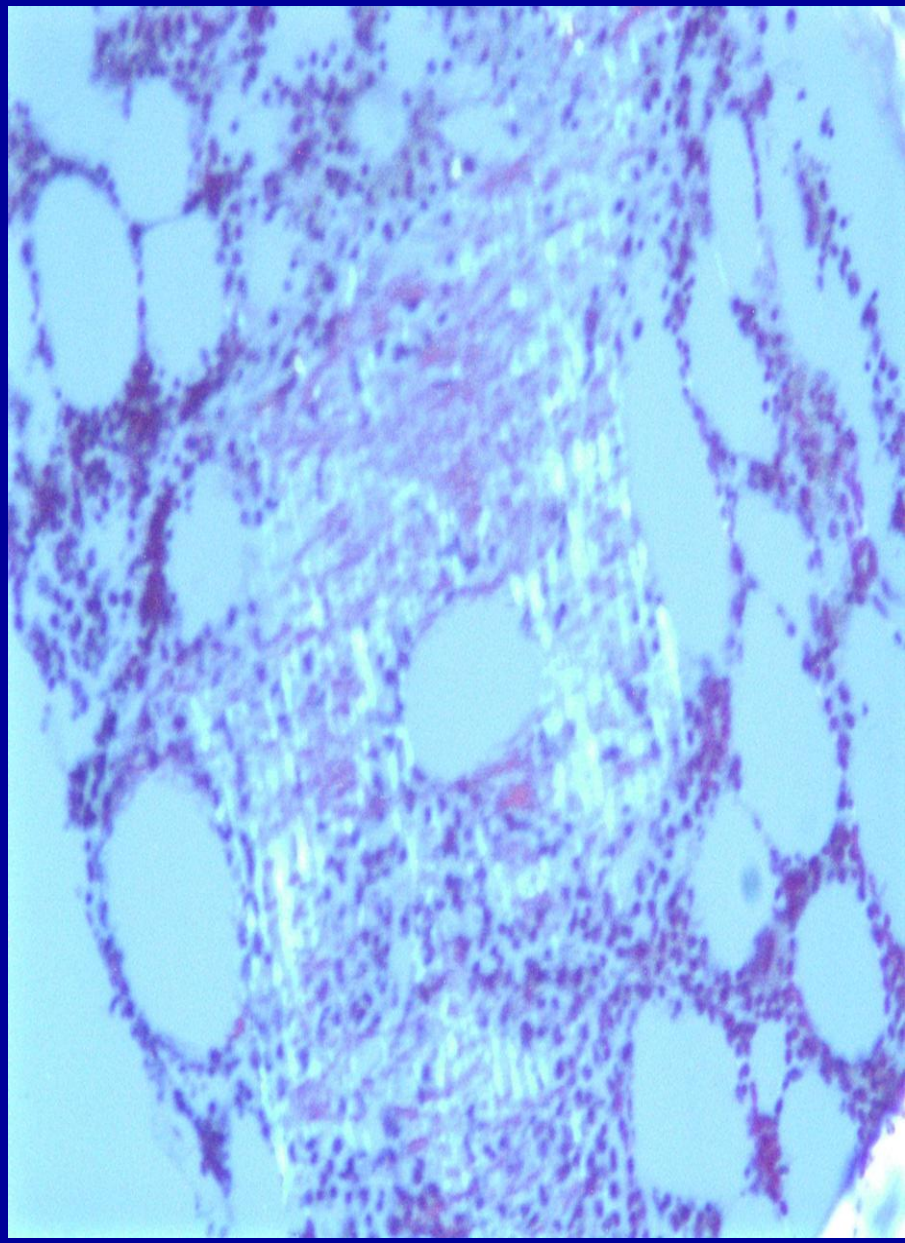
- also show less than 10 % marrow plasma cells
- no skeletal lesions
- Bence Jones proteinuria and low serum paraprotein may occur
- Treatment as for myeloma beneficial
- 10 % all plasma cell dyscrasias
- SPEP + in 90 - 95 %





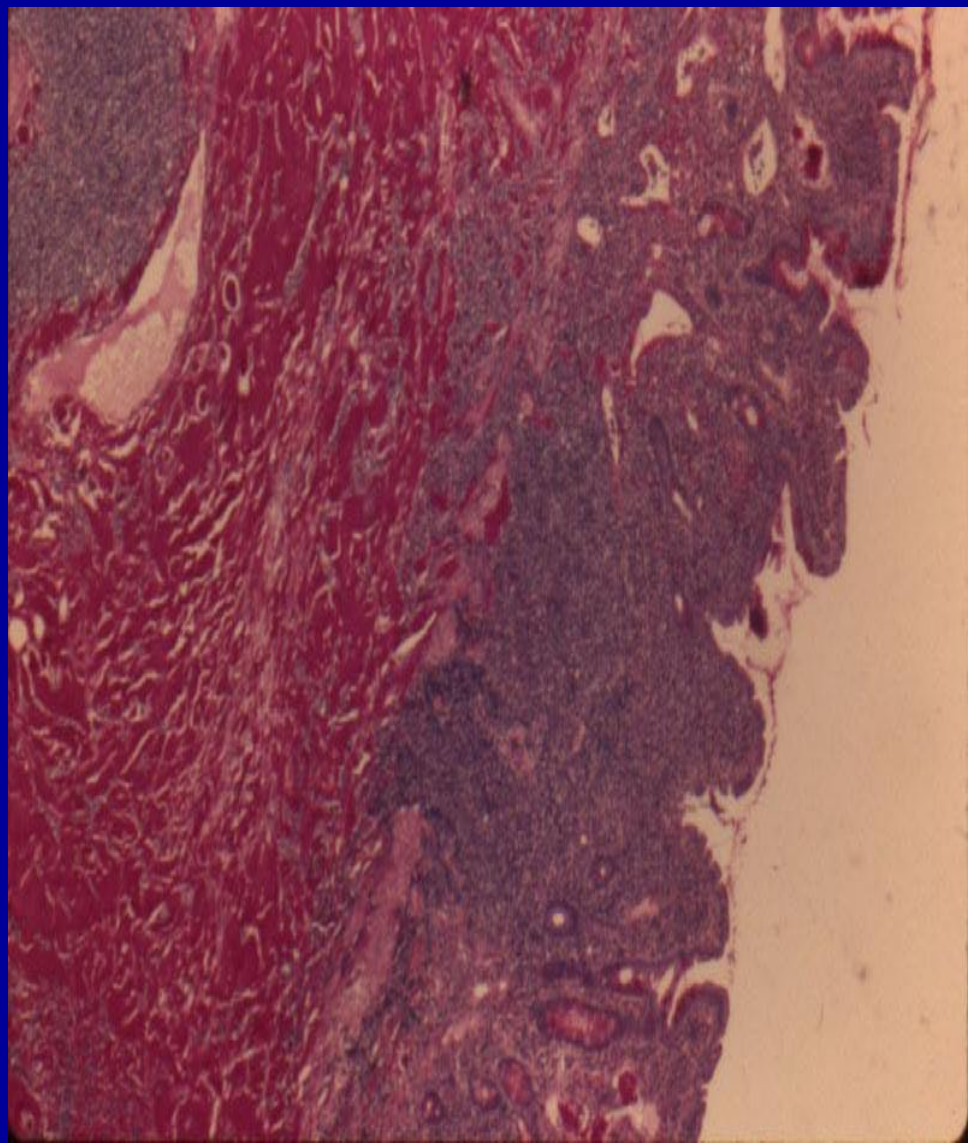






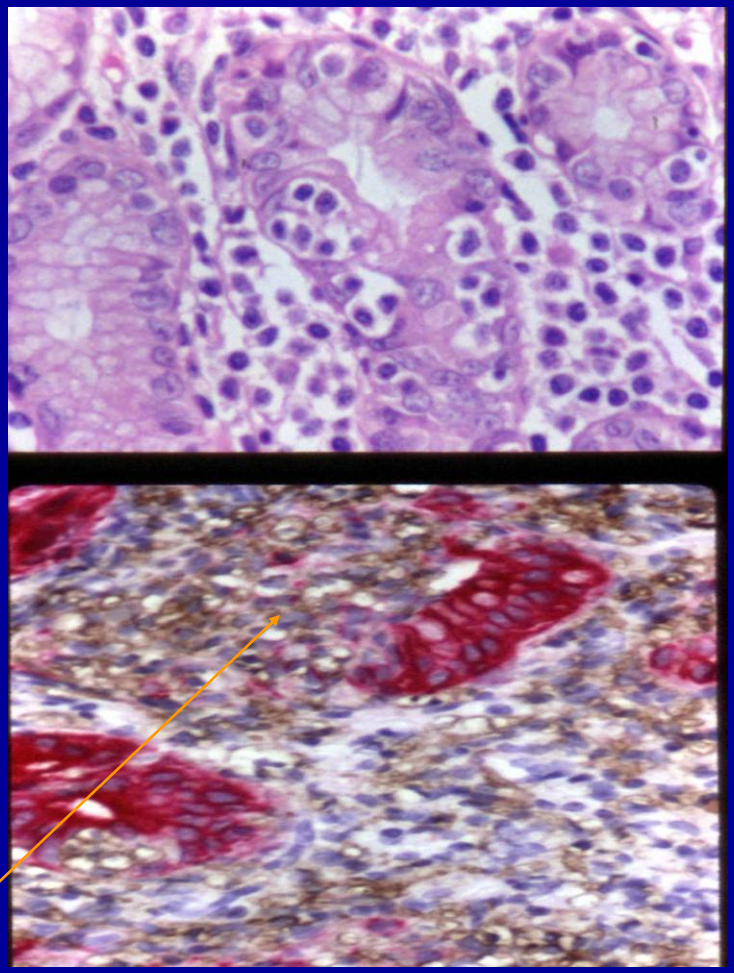
Immunoglobulin deposition diseases

- rare
- Congo red negative
- renal or heart diseases due to protein deposits in tissues
- renal biopsy-Dx
- SPEP + 70-85 %



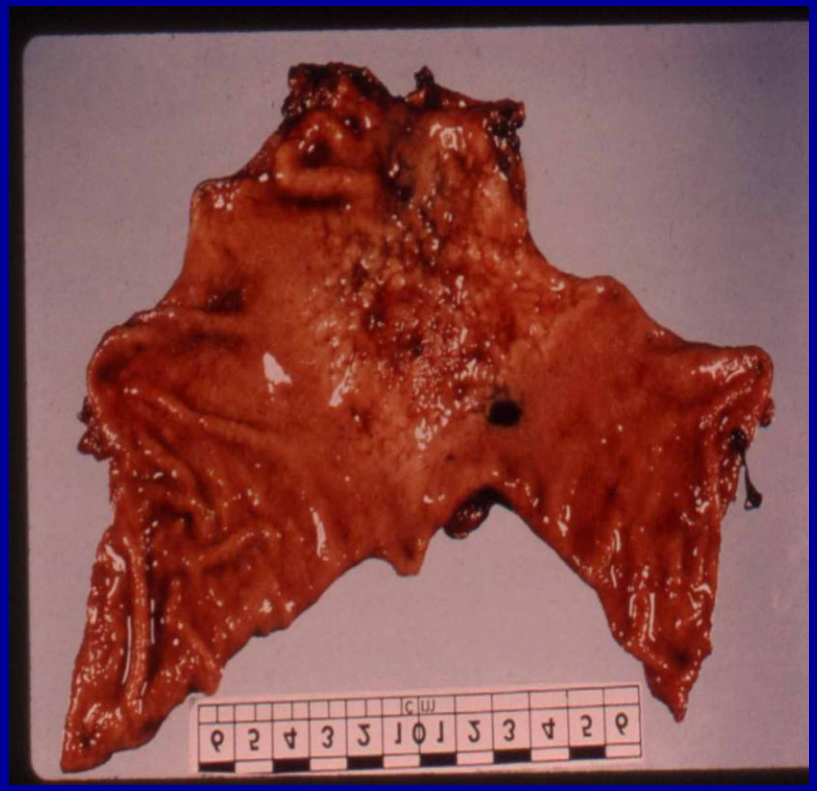
MALT lymphoma

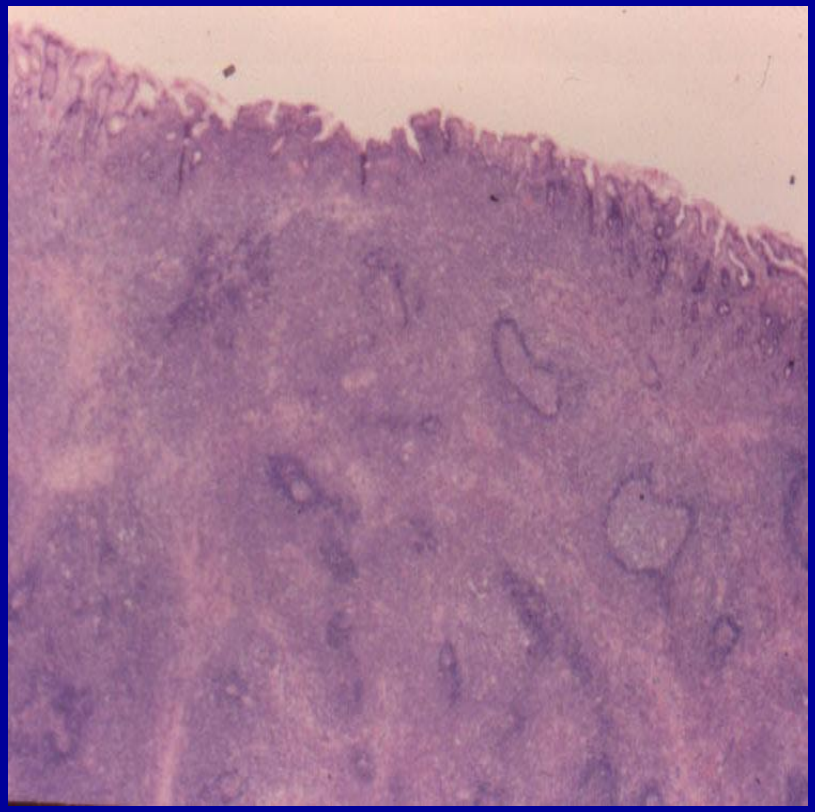
- Prototype of extra-nodal lymphoma with distinctive biologic localization to mucosal tissues
- H. pylori bacteria + in Gastric lesions
- low grade , absent BM involvement
- 80% survival in 15 yrs



Lympho-epithelial
B-cell lesions

Lymphoepithelial lesions and Pseudolymphoma

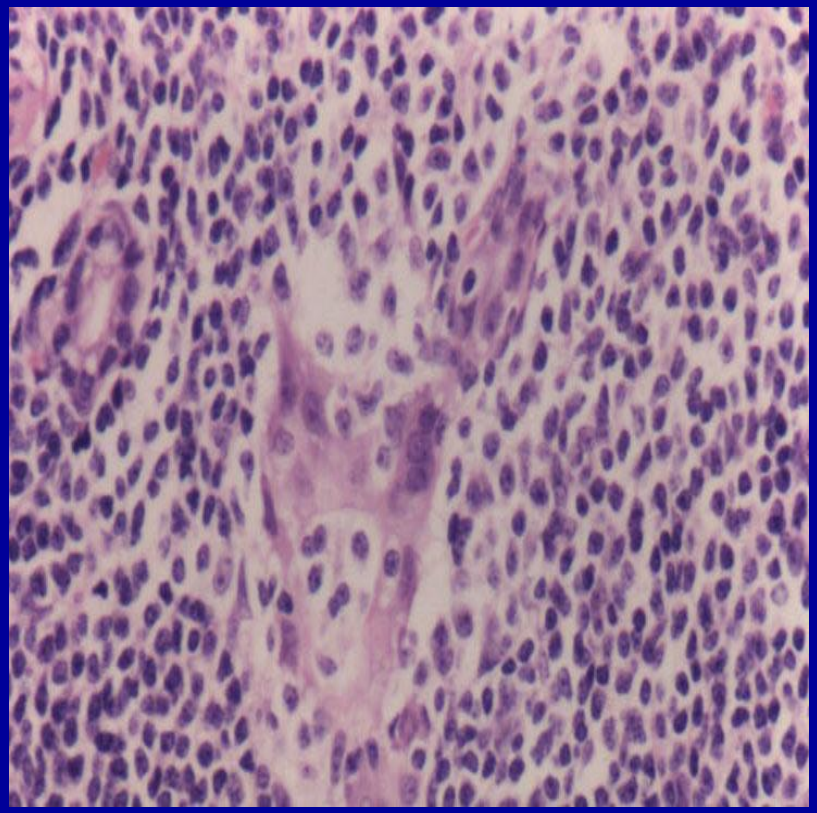


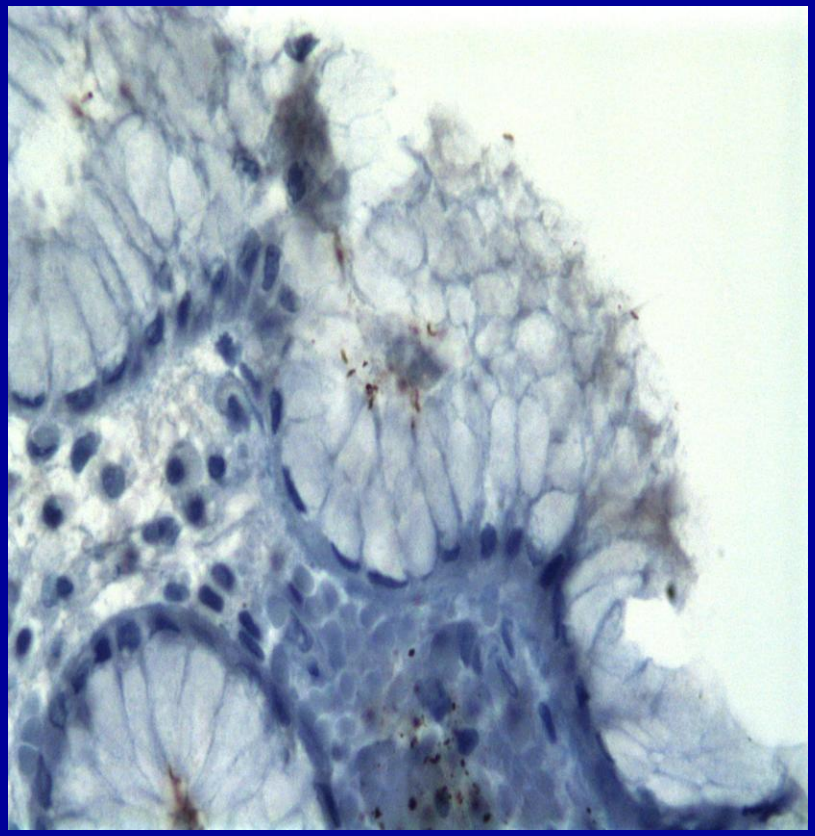


Cytologic patterns

- Small centrocyte like
- Small lymphocytes
- Monocytoid cells
- Plasma cells monoclonal in one third
- Follicular colonization of benign germinal centers
- Wootherspoon’s grading 0 to 5

LELs and H pylori



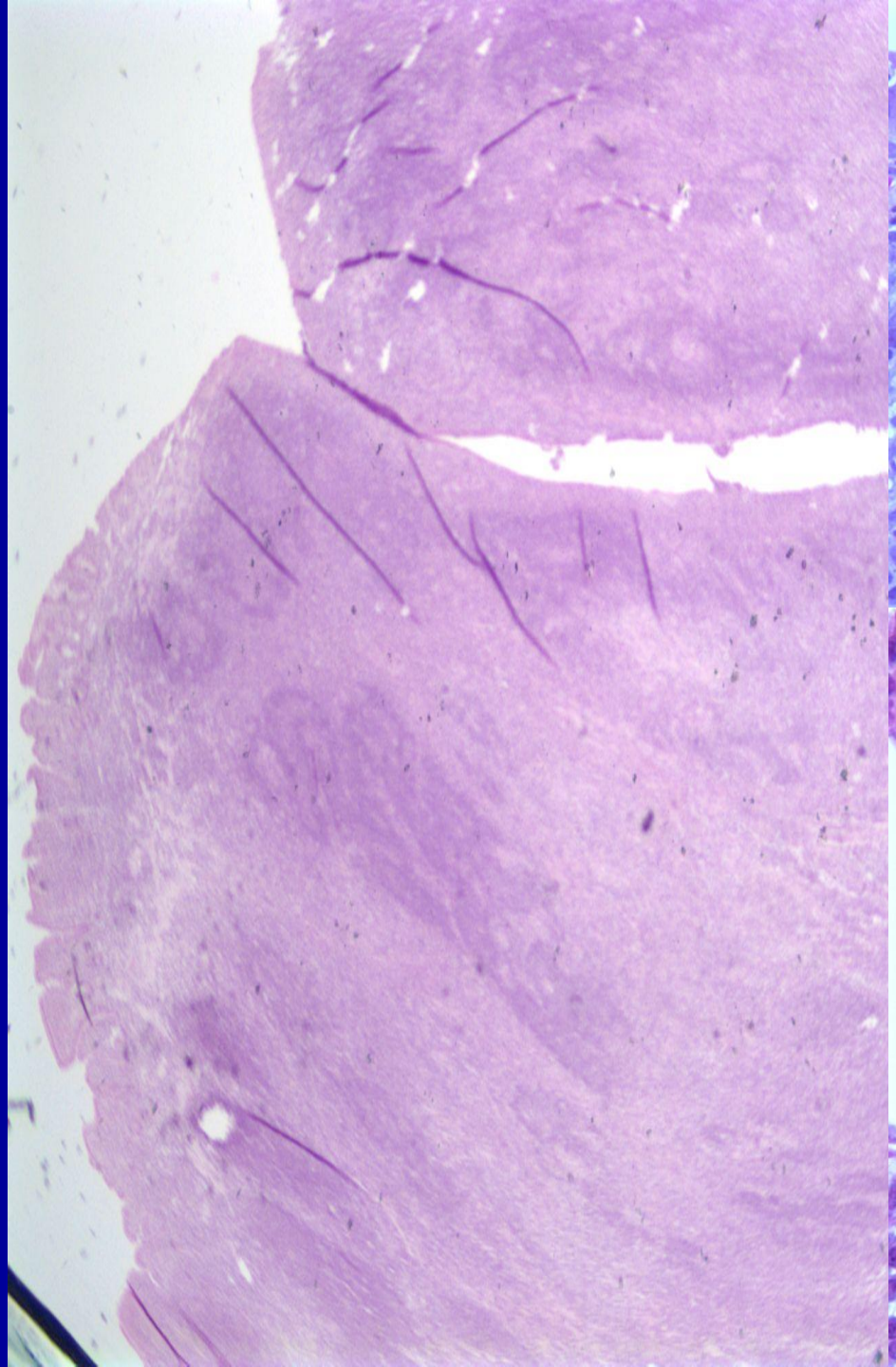
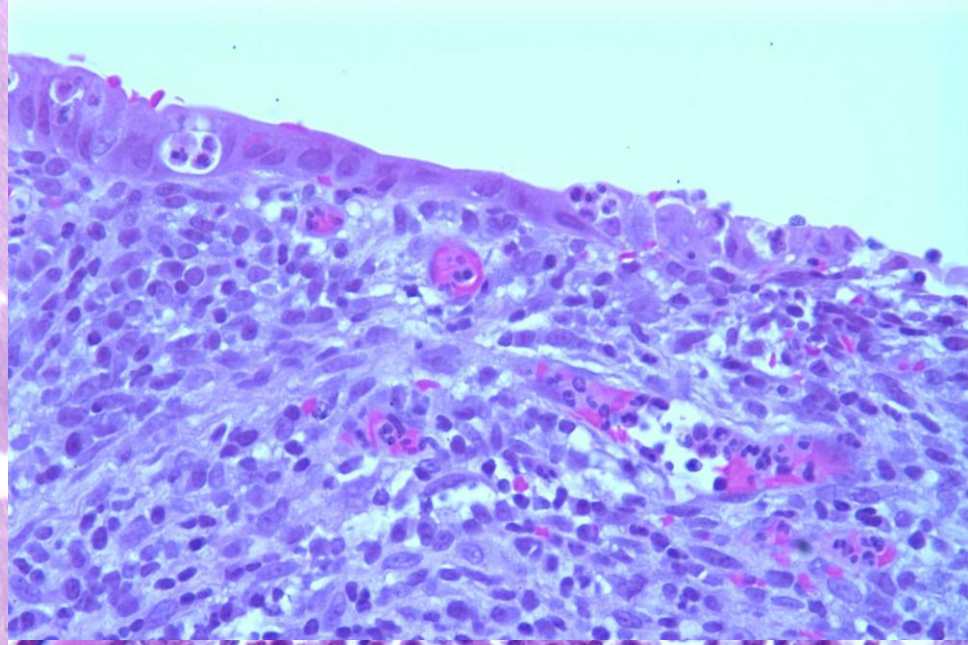
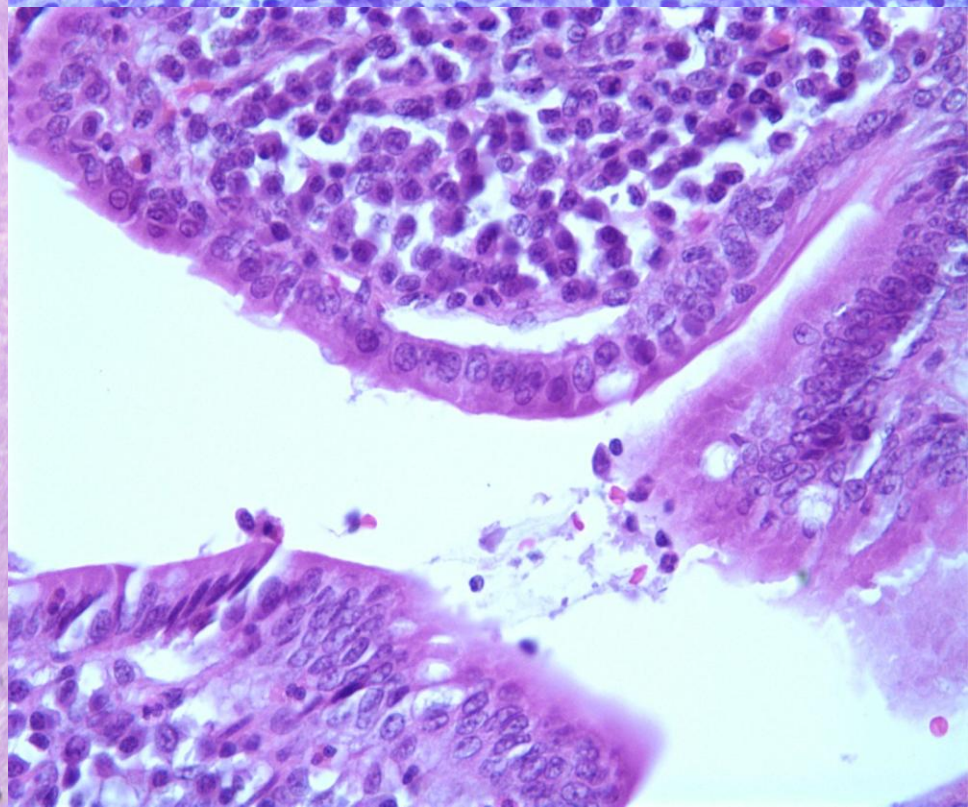


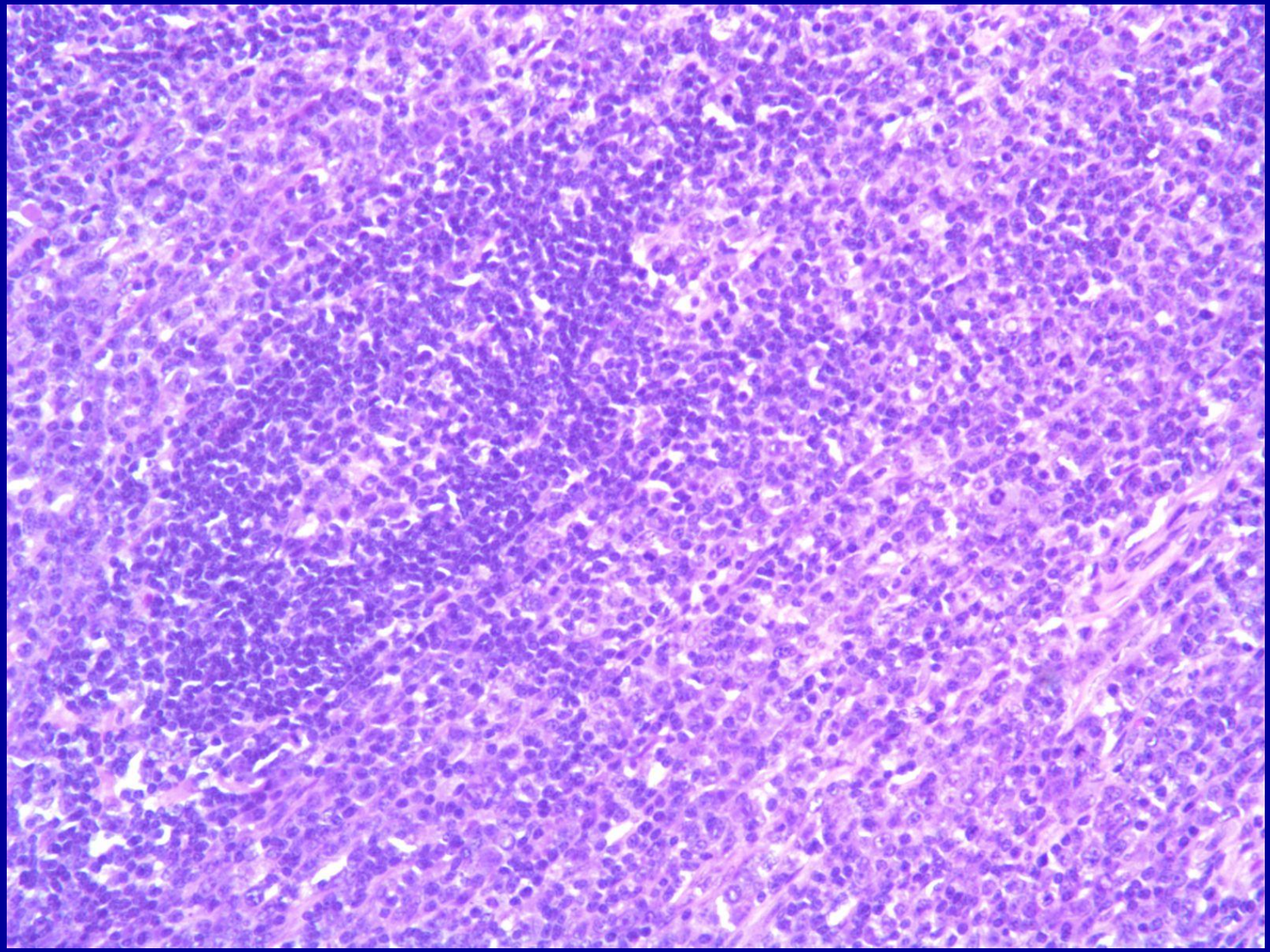
Molecular lesions

- T 11;18 q21 q21 API2- MALT 25 %
  - H pylori independent
- T 1;14 bcl10
- and t14;18 MALT1
- and t 3;14 Foxp1
- Involvement of BCL10 and NFkB pathways

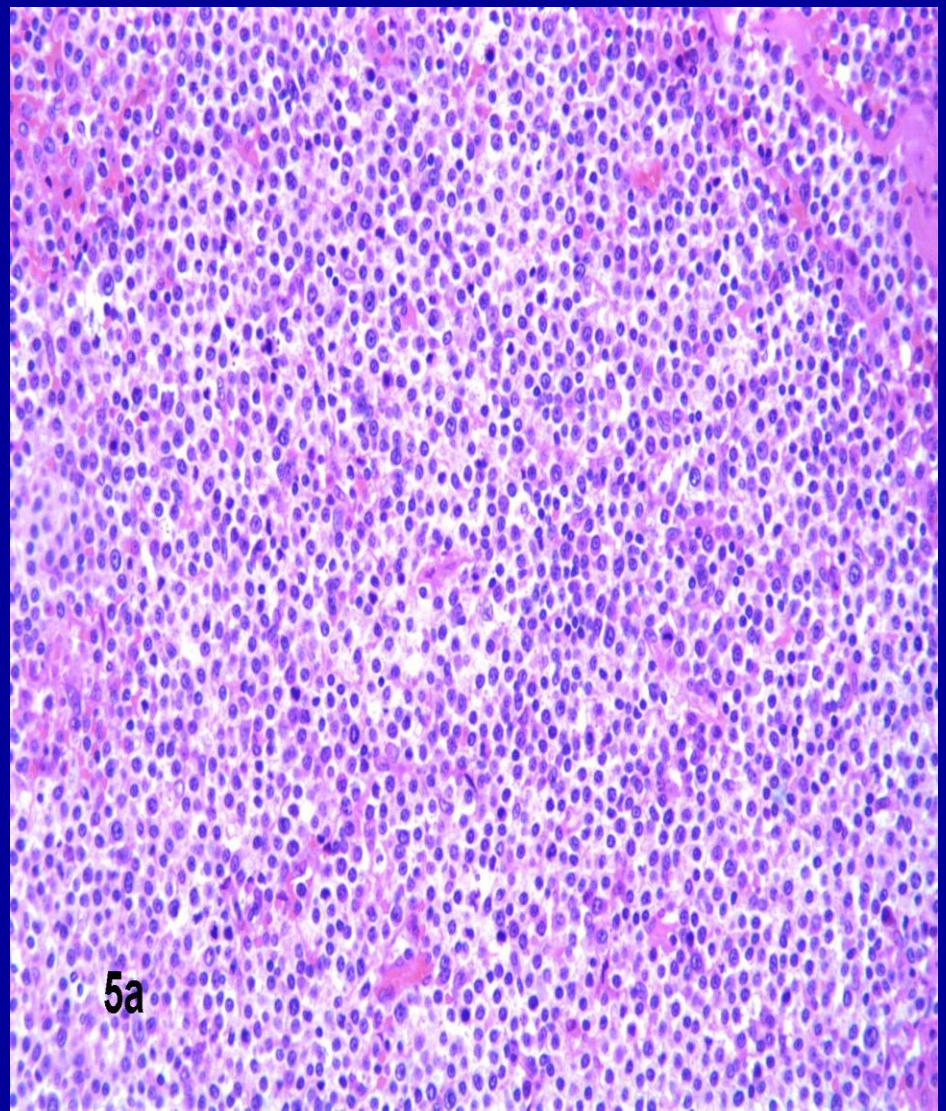
MALTOMA and infection

- H pylori in Gastric MALT
- C. psitacci in Ocular MALT
- C. jejuni in IPSID or Intestinal MALT
- Hepatitis C in Splenic MZL and Salivary MALT



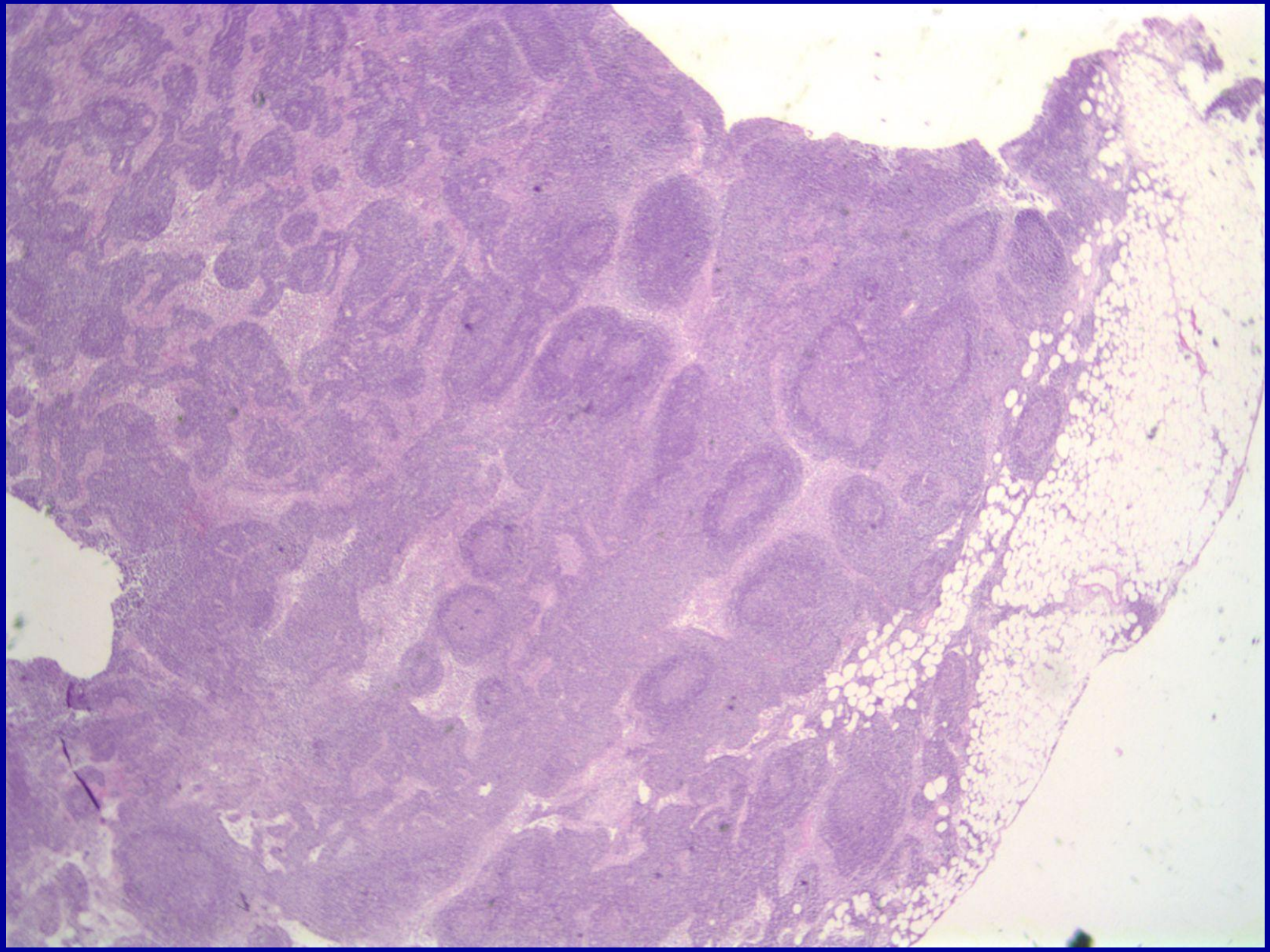
Nodal Marginal Zone Lymphoma

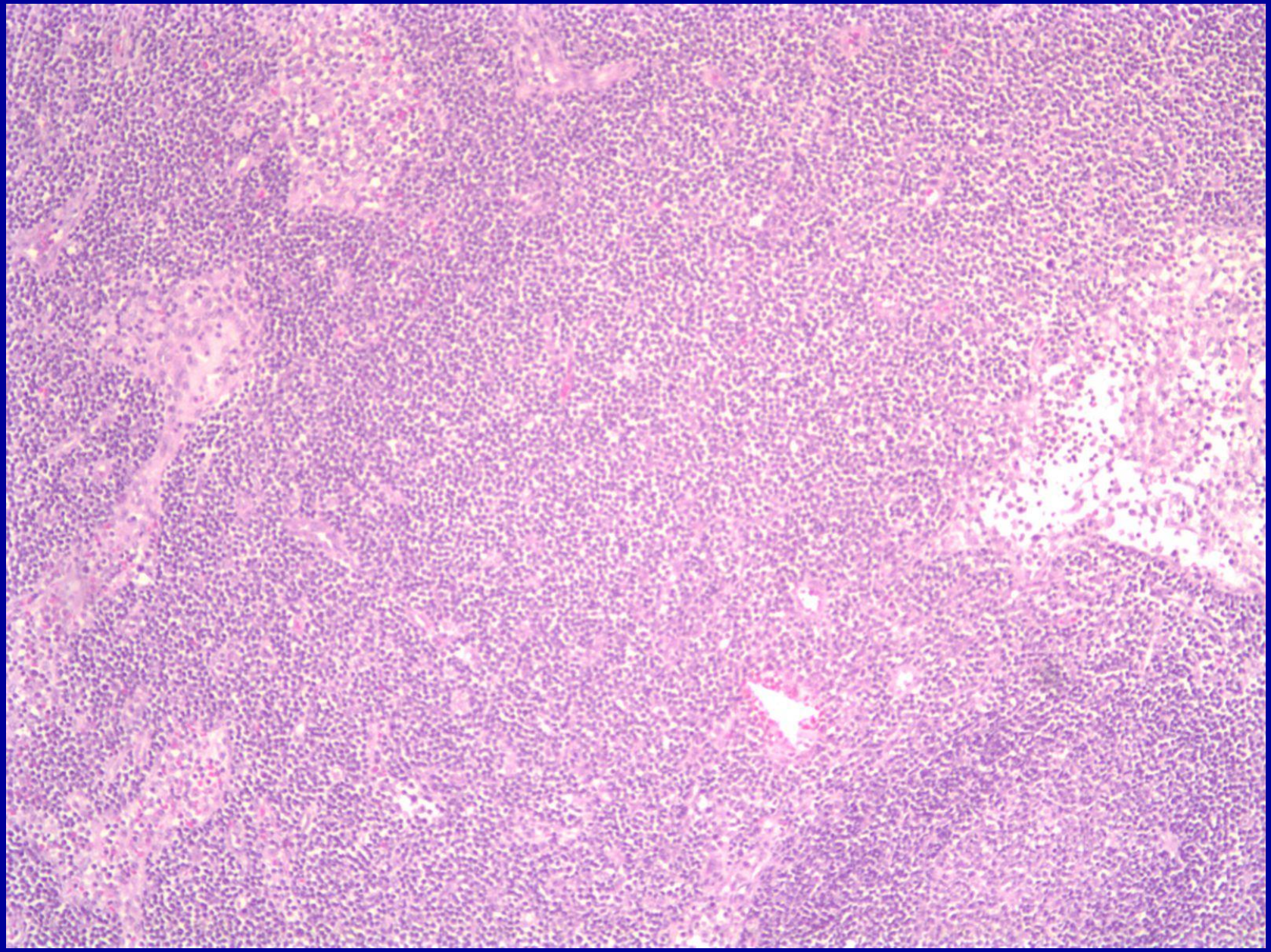


- 1.8% of all lymphomas
- Diffuse or nodular
- Monocytoid cells
- CD5-,CD10-
- Guarded prognosis
- Extranodal lymphoma in one third of cases

Prognosis

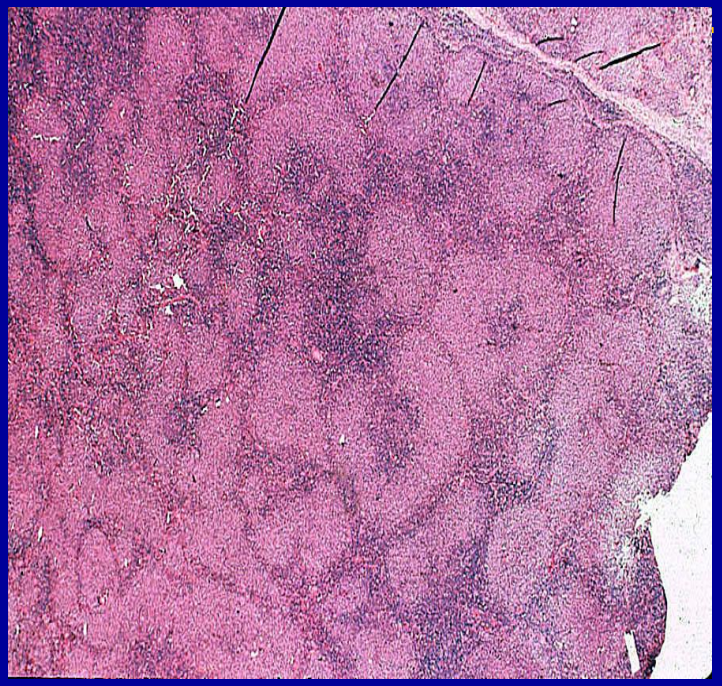
- Patients with nodal MZL present with more advance disease (71%) and BM involvement (28%),
- 5-year overall survival rate of 56% and a failure-free survival rate of only 28%.
- Histologic transformation to a higher-grade lymphoma occurs in more than 20% of cases.
- In ~70% of nodal MZL, there is no involvement of spleen or extranodal sites.



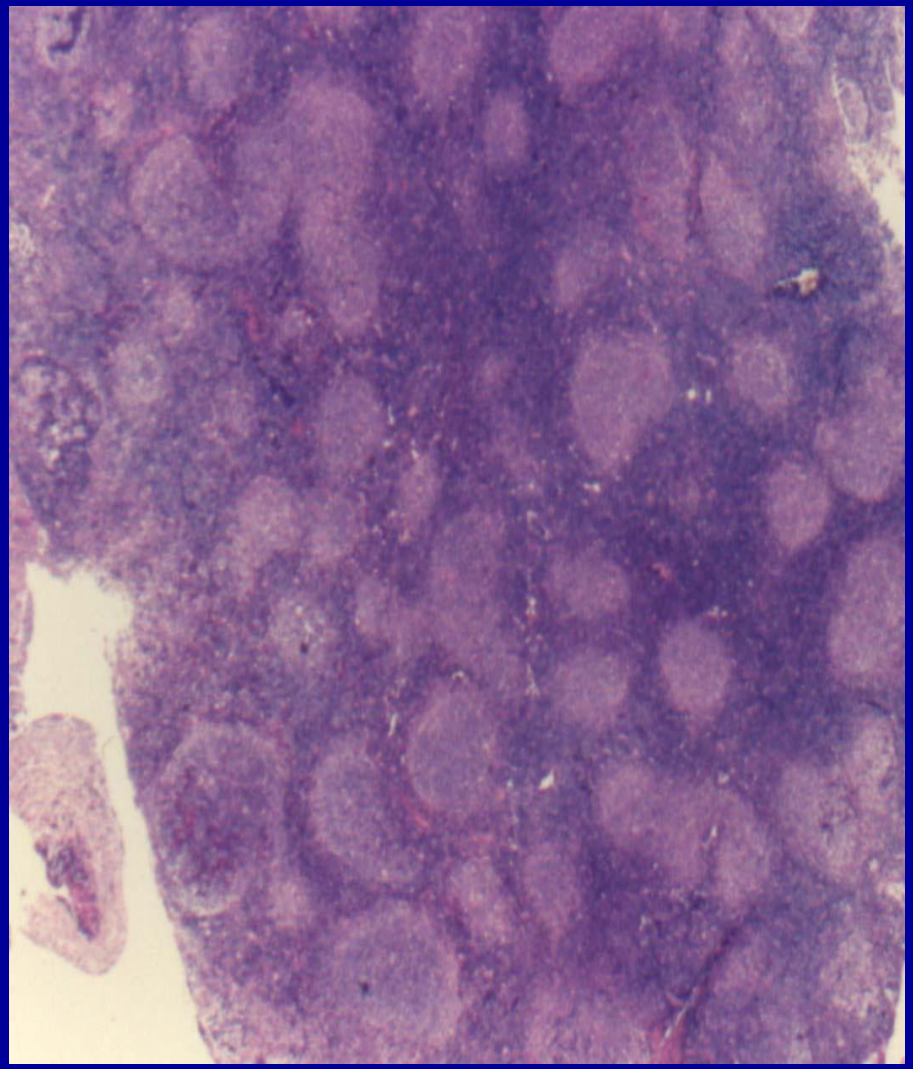


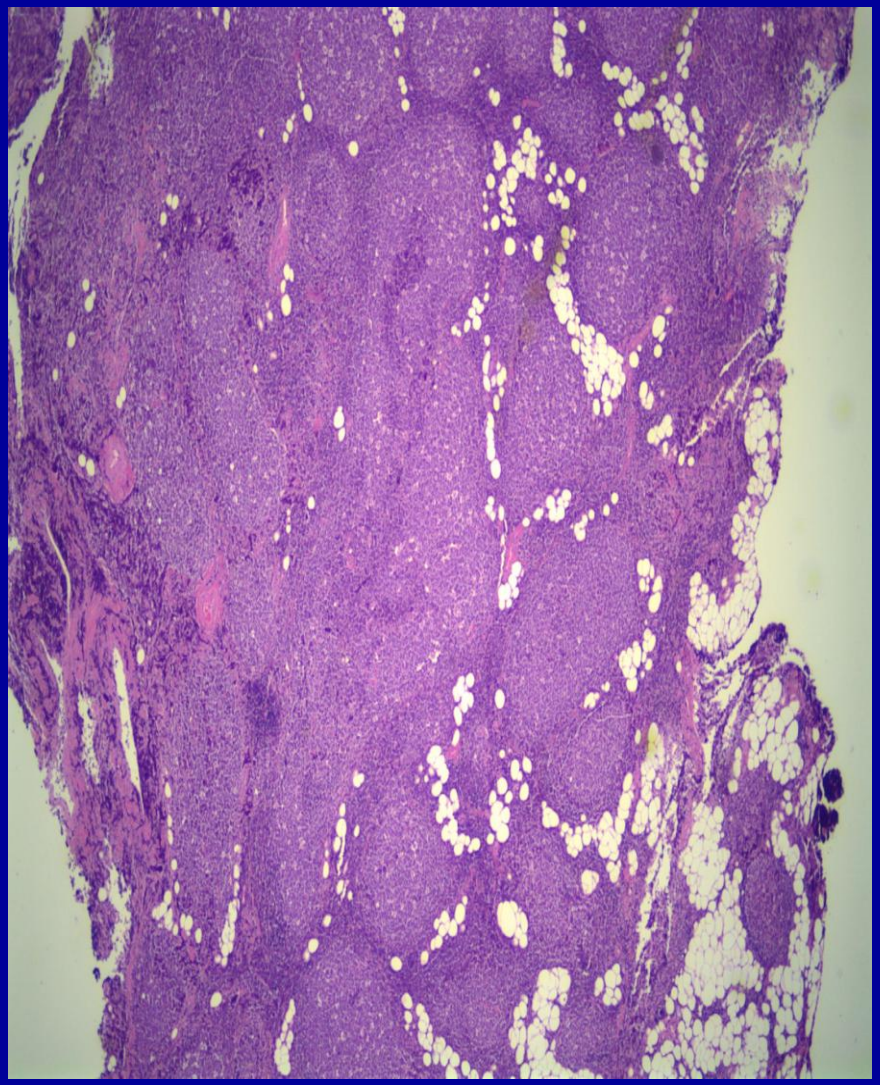
Follicular lymphoma

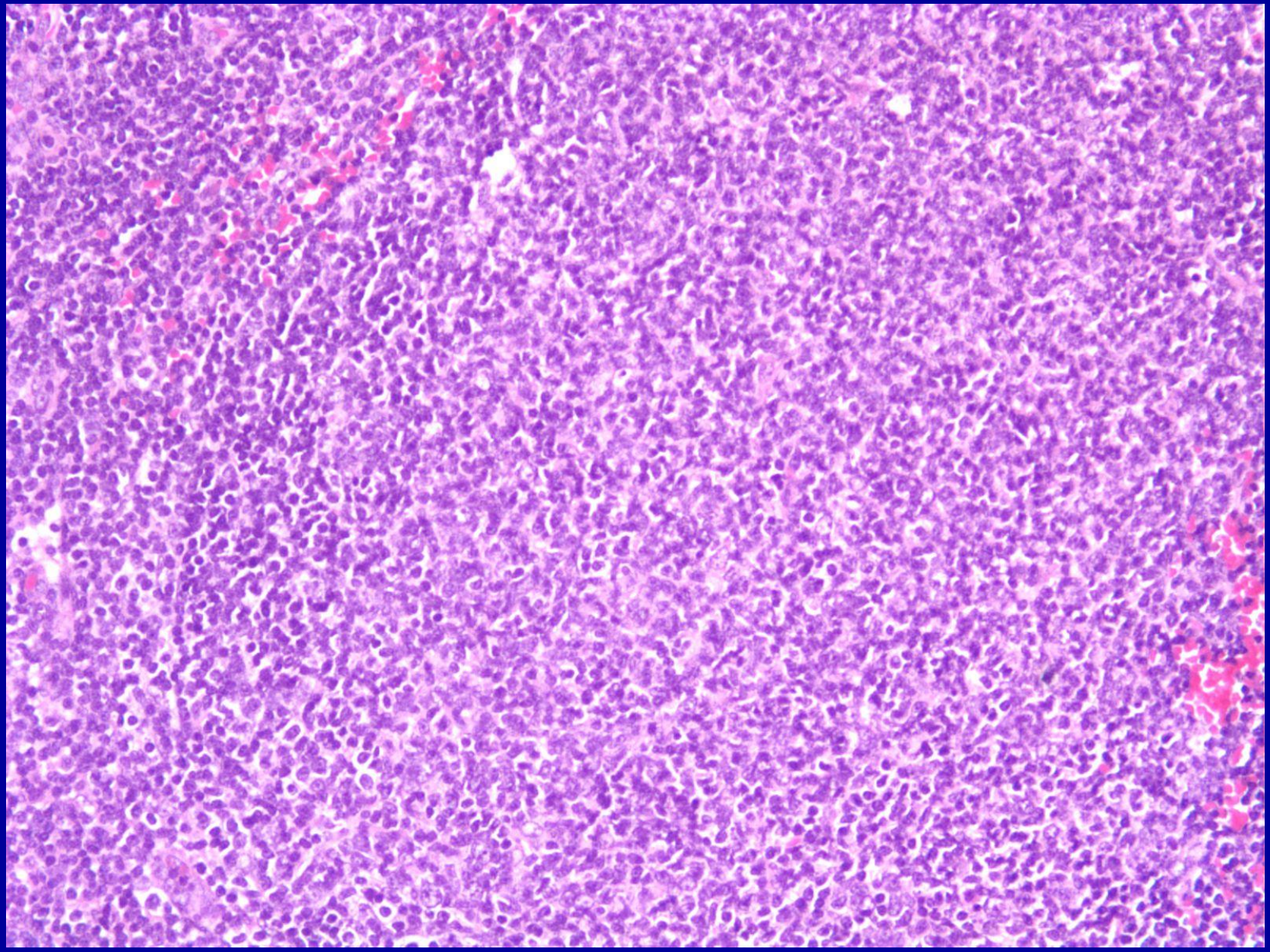
- Back to back

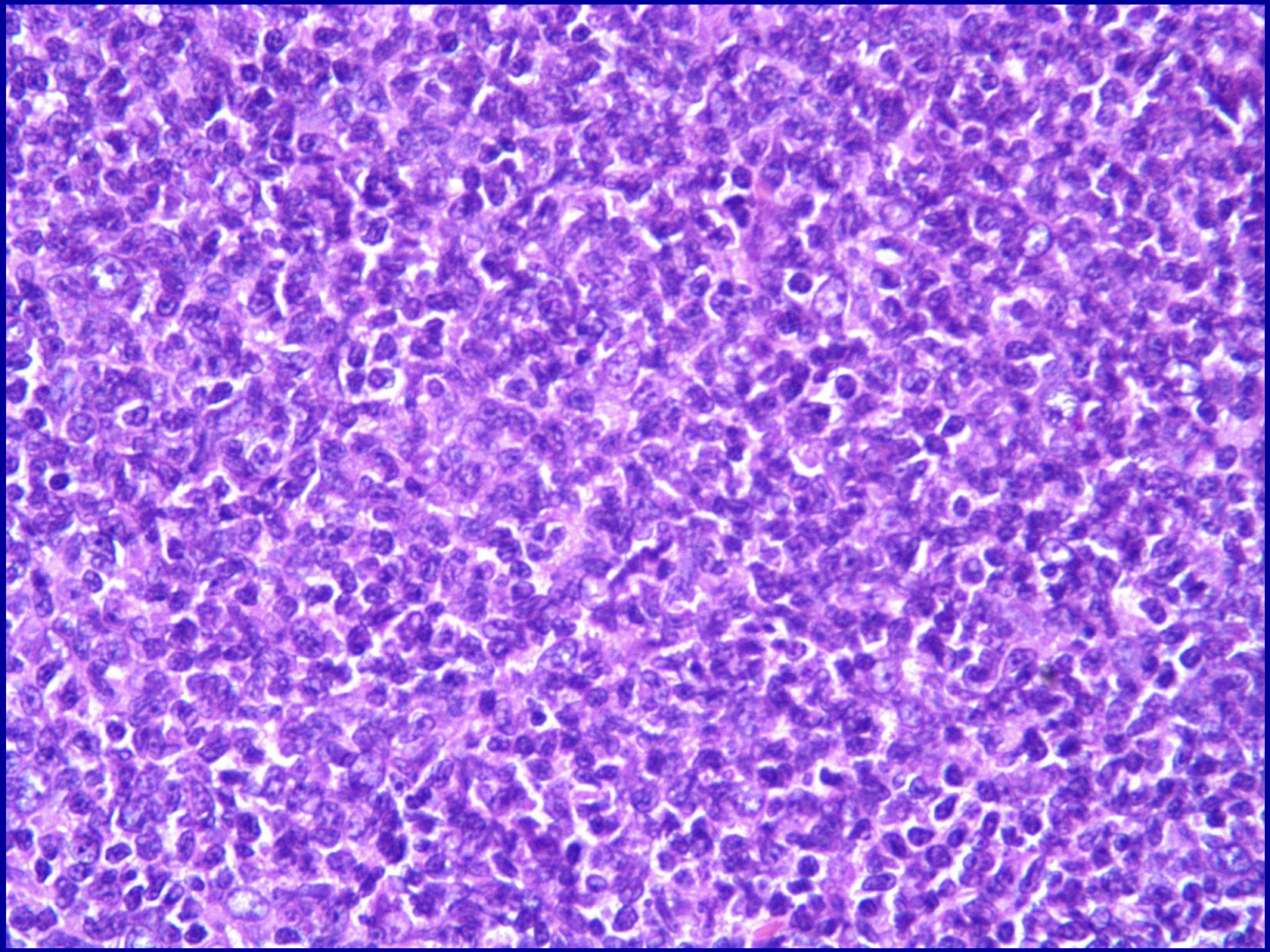


Follicular pattern

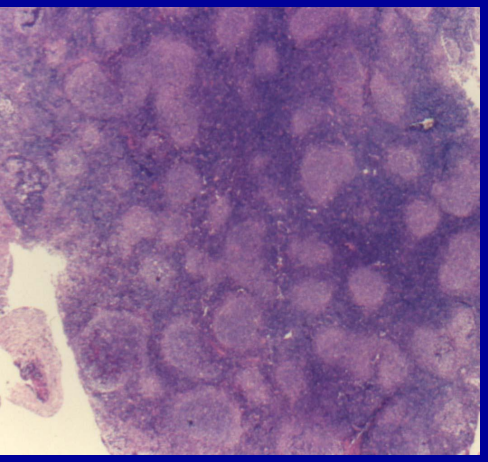


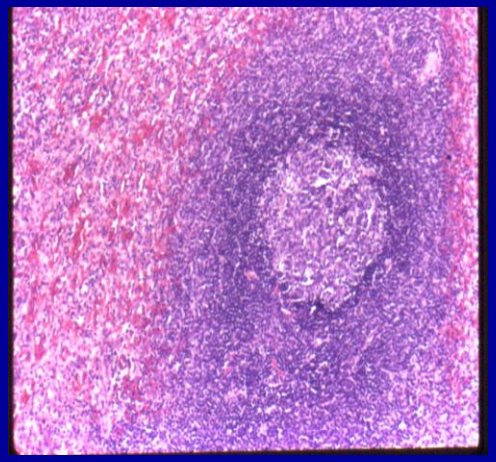


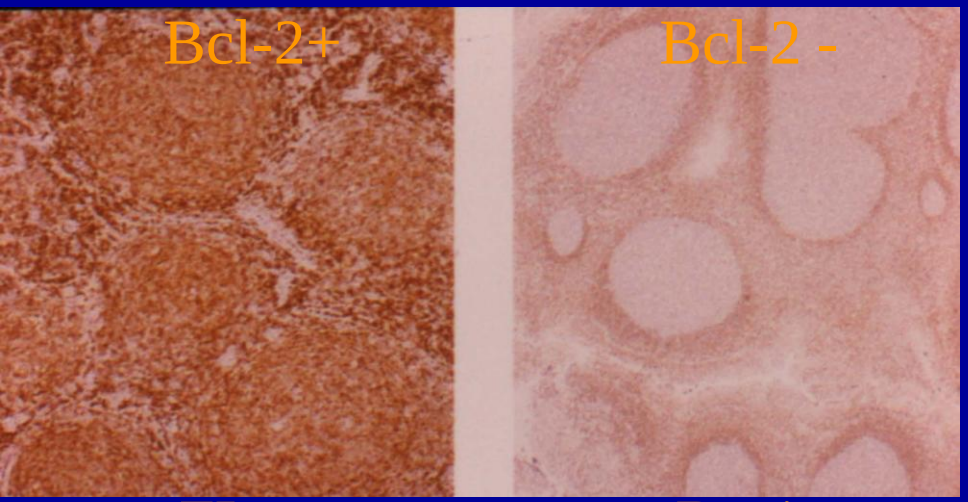




Follicular lymphoma







FL Benign

- follicle center cell with CD19+, CD10+,BCl6+, Bcl-2+ small cleaved lymphocytes forming follicular pattern common
- low grade indolent
- difficult to cure
- t14;18---bcl-2 oncogene

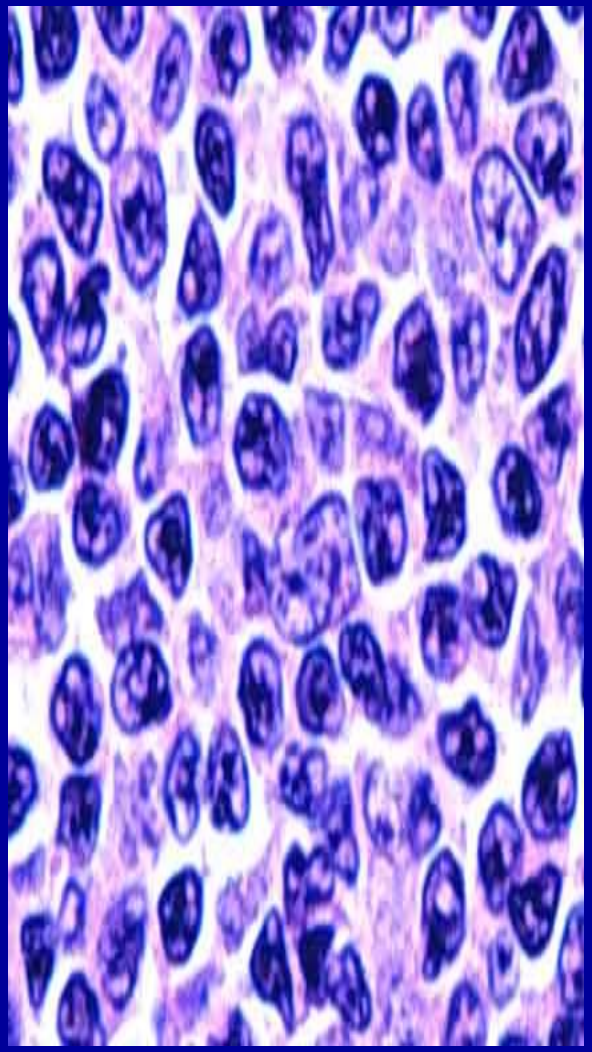
WHO Grading of FL

Table 6.13
Follicular lymphoma: grading and variants.

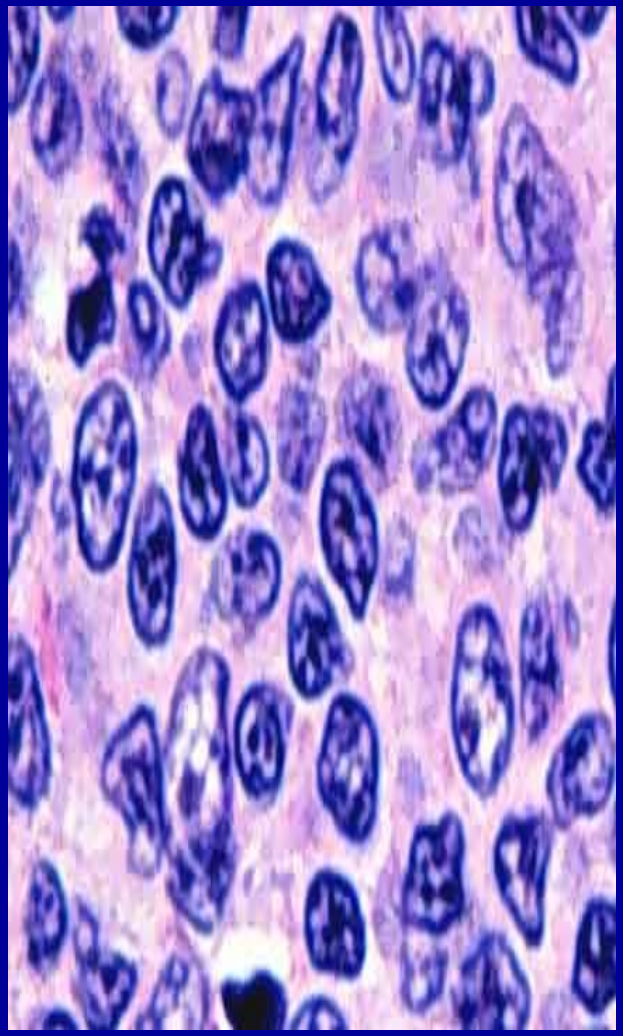
Grading	**Definition**
Grade 1	0-5 centroblasts per hpf*
Grade 2	6-15 centroblasts per hpf*
Grade 3	>15 centroblasts per hpf*
3a	Centrocytes present
3b	Solid sheets of centroblasts
Reporting of pattern	**Proportion follicular**
Follicular	>75%
Follicular and diffuse	25-75% **
Focally follicular	<25% **
Follicular lymphoma: variants	
Diffuse follicle centre lymphoma	
Grade 1	0-5 centroblasts/hpf*
Grade 2	6-15 centroblasts/hpf*
Cutaneous follicle centre lymphoma	(see text for definition)

*hpf = high-power field of 0.159 mm2 (40X objective, 18 mm field of view ocular; count 10 hpf and divide by 10). If using a 10 mm field of view ocular, count 8 hpf and divide by 10 or count 10 hpf and divide by 12 to get the number of centroblasts/0.159 mm2 hpf.
If using a 22 mm field of view ocular, count 7 hpf and divide by 10 or count 10 hpf and divide by 15 to get the number

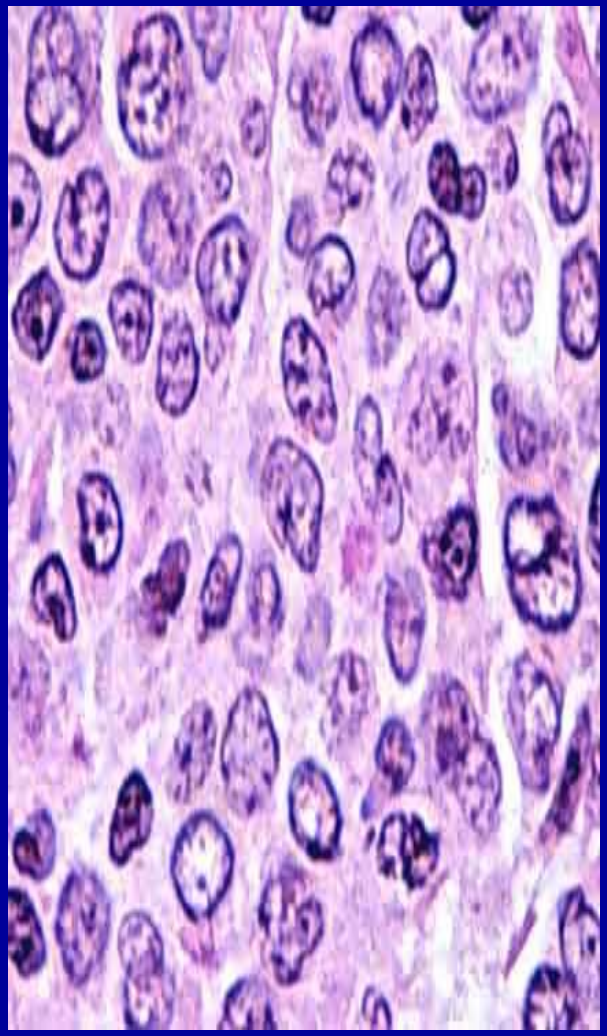
Grade I



Grade II



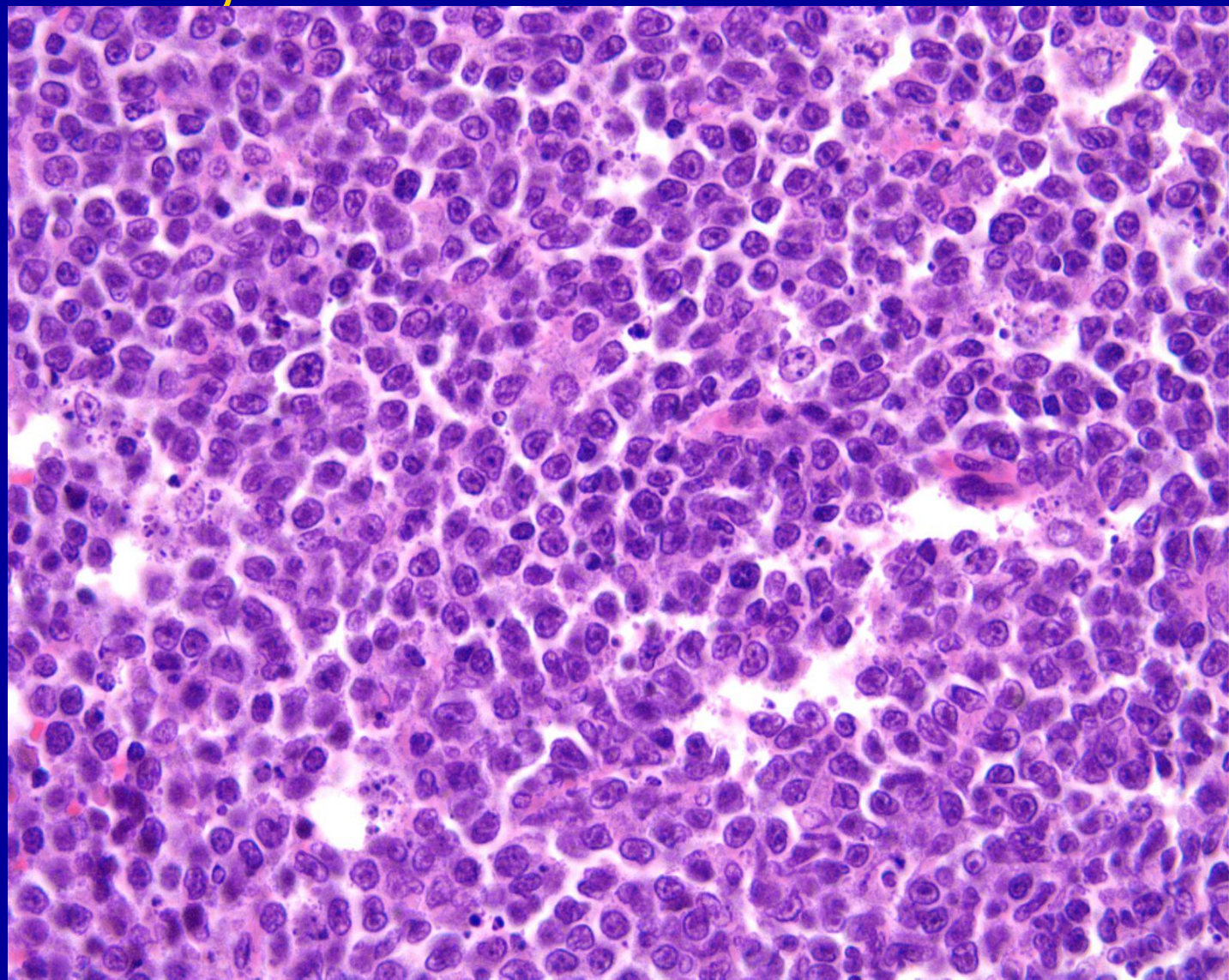
Grade III A



FL, Grade IIIb

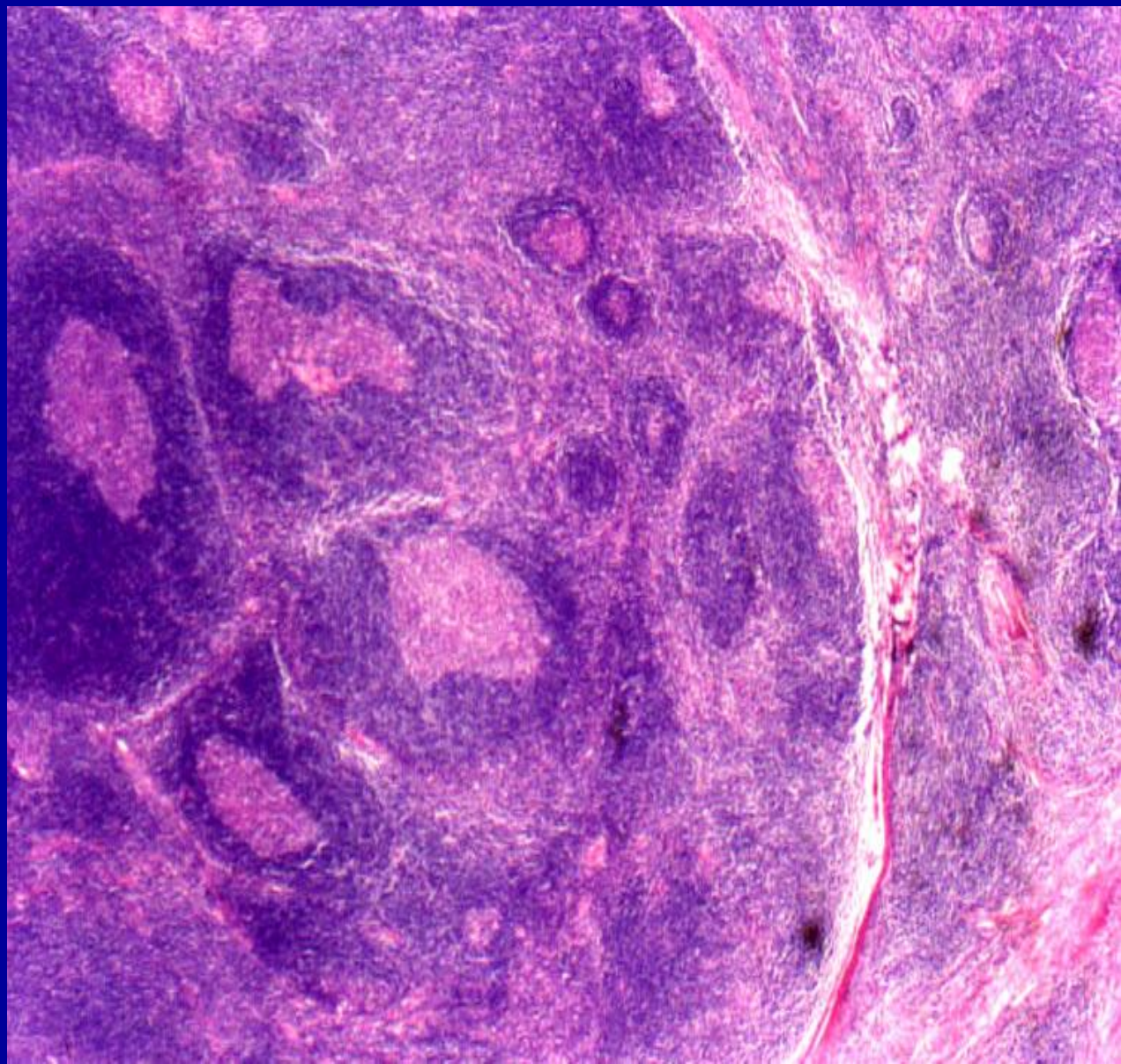
- Sheets of large cells
- Presence of

Diffuse large B-cell areas worse than FL grade IIIa

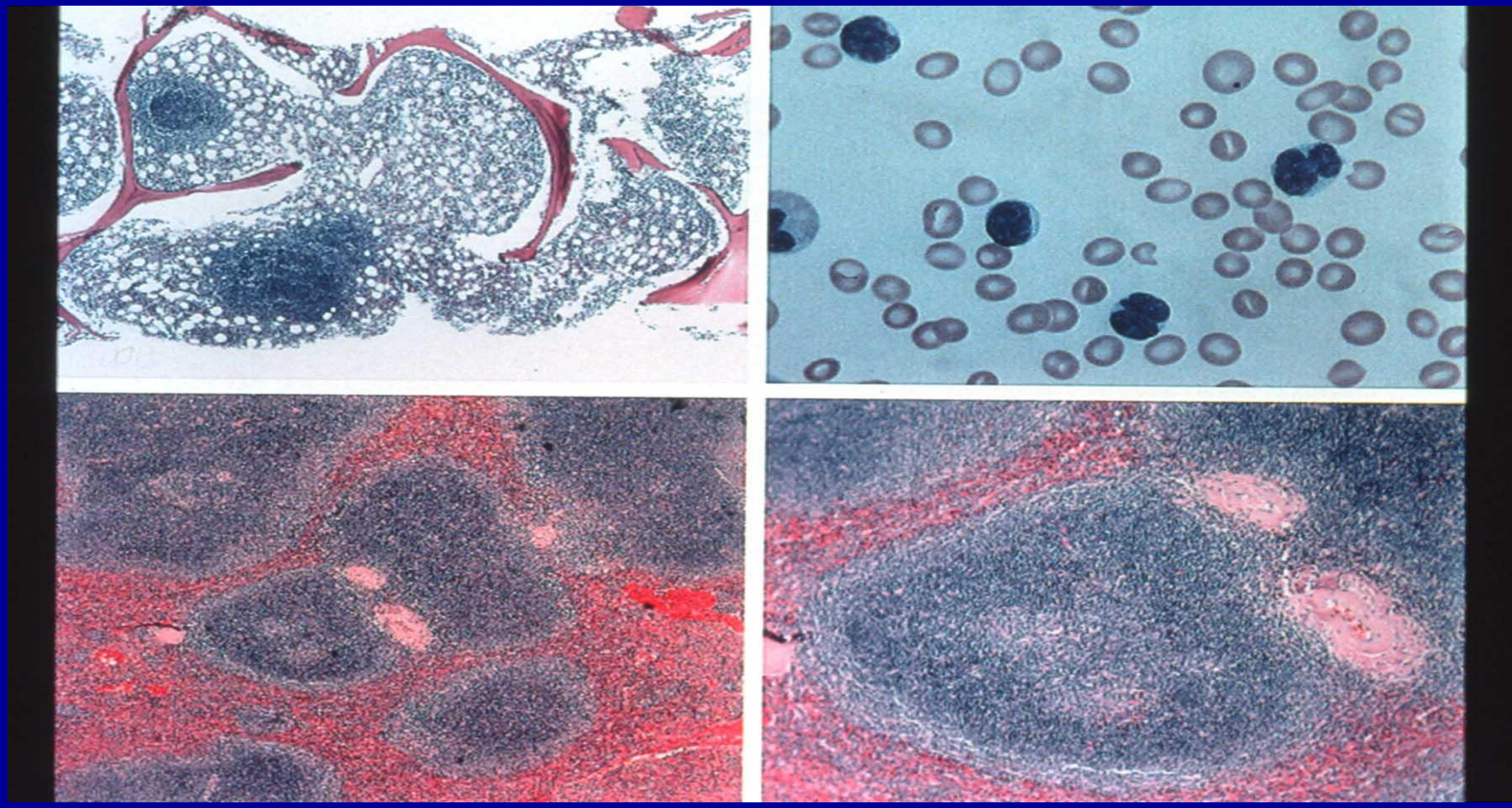


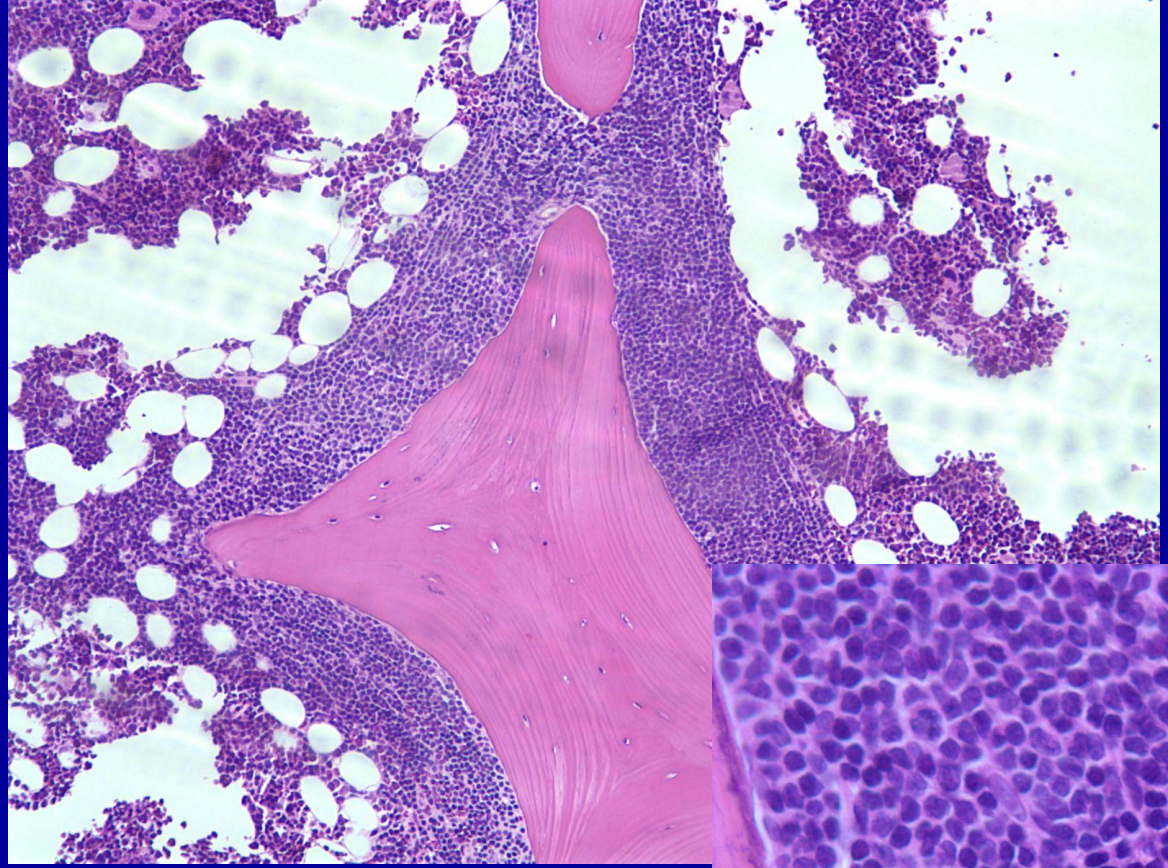
mantle zone pattern

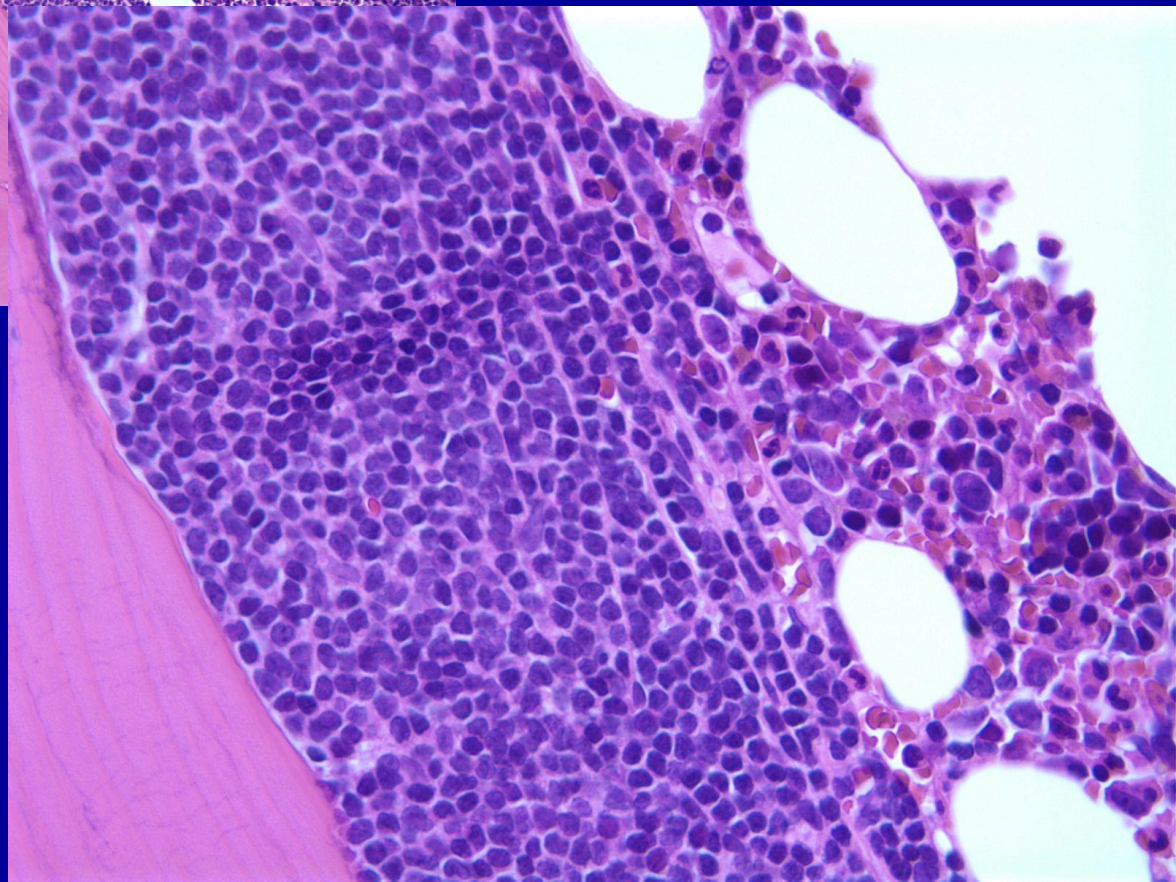
- Mantle zone hyperplasia
- rule out
  - mantle cell lymphoma
  - marginal zone lymphoma



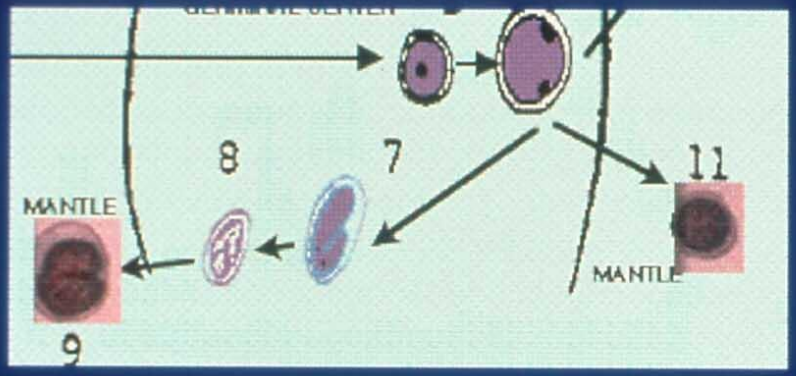
Mantle cell pattern prototype is mantle cell lymphoma







mantle cell lymphoma



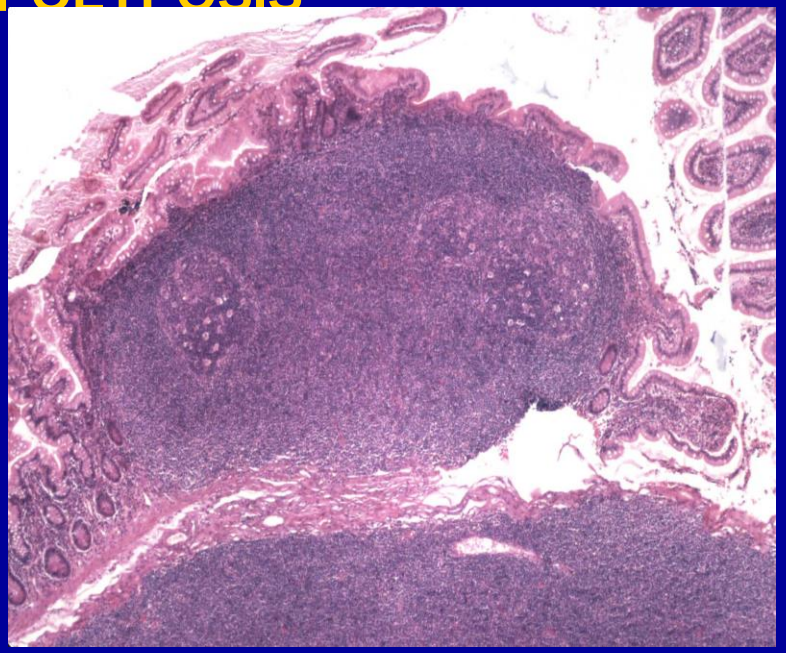
INTERMEDIATE CELL LYMPHOMAS
-PREVIOUSLY CALLED SMALL LYMPHOCYTIC, FSC, DIFFUSE SMALL CLEAVED

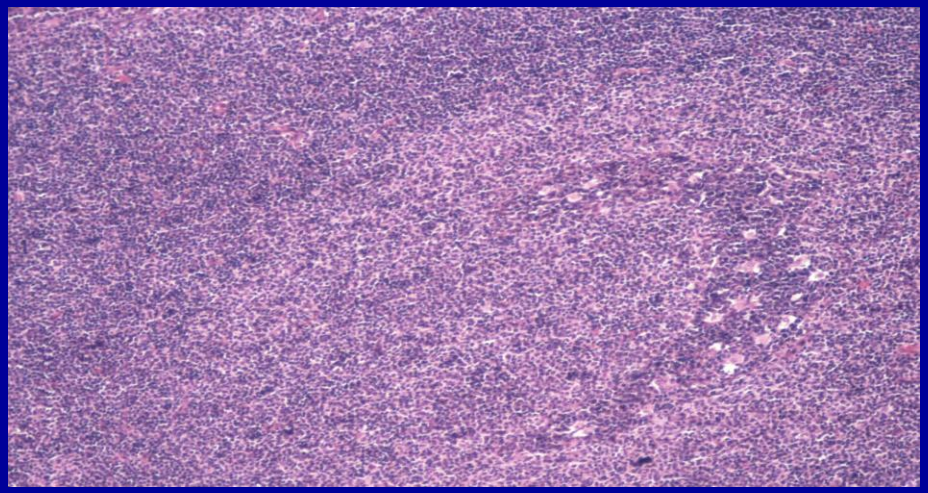
CD5+, t(11;14) -- nuclear cyclin D1
about 10 % of all NHL
spleen, bone marrow, GIT frequently involved

Median survival is significantly worse than other lymphomas of favorable subtypes grouped together(WF A-E): 3 vs 8 yrs

MCL not curable using CHOP; 6 % survive 10 years or longer

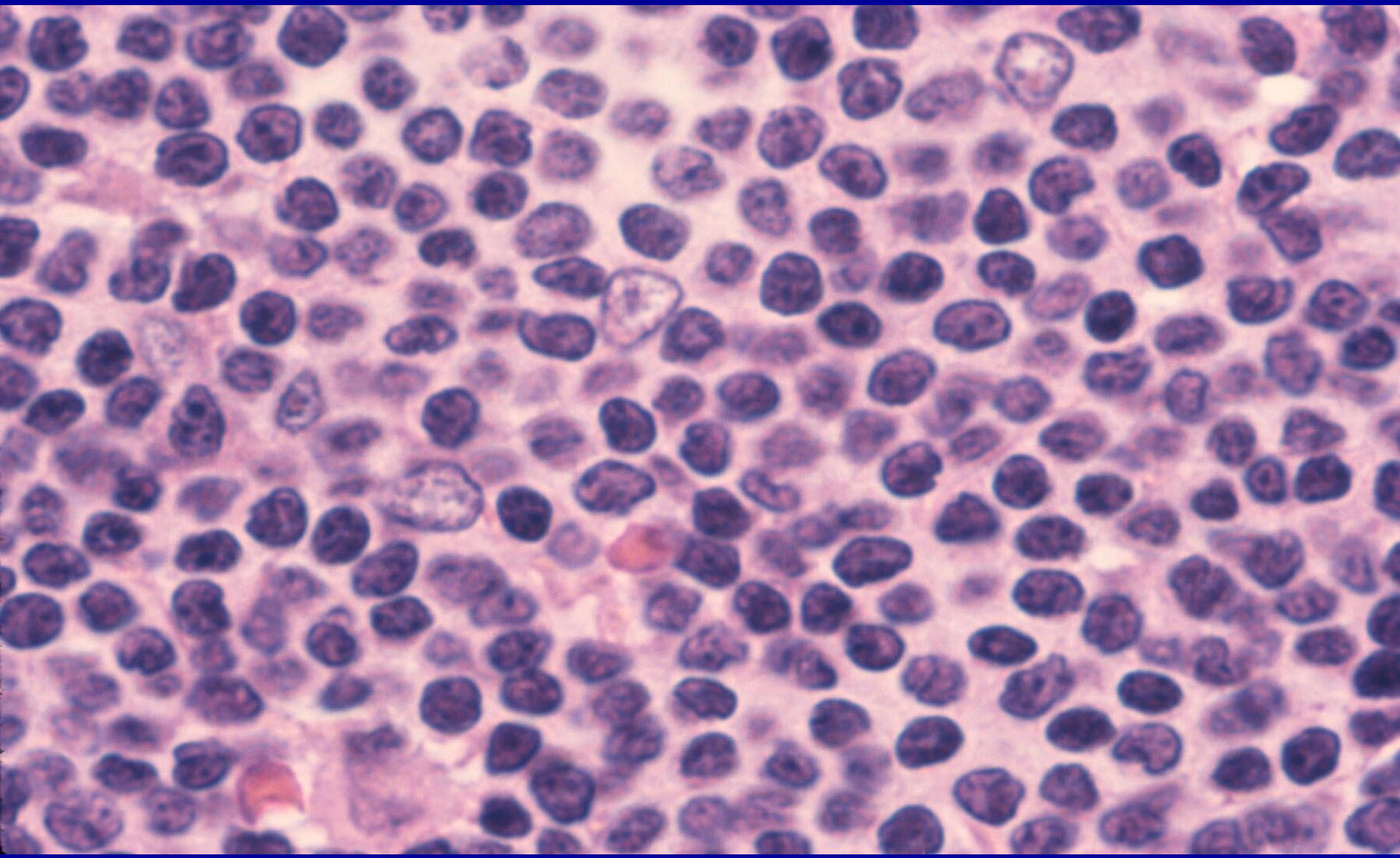
EXTRANODAL Mantle cell Lymphoma- multiple LYMPHOMATOUS POLYPOSIS



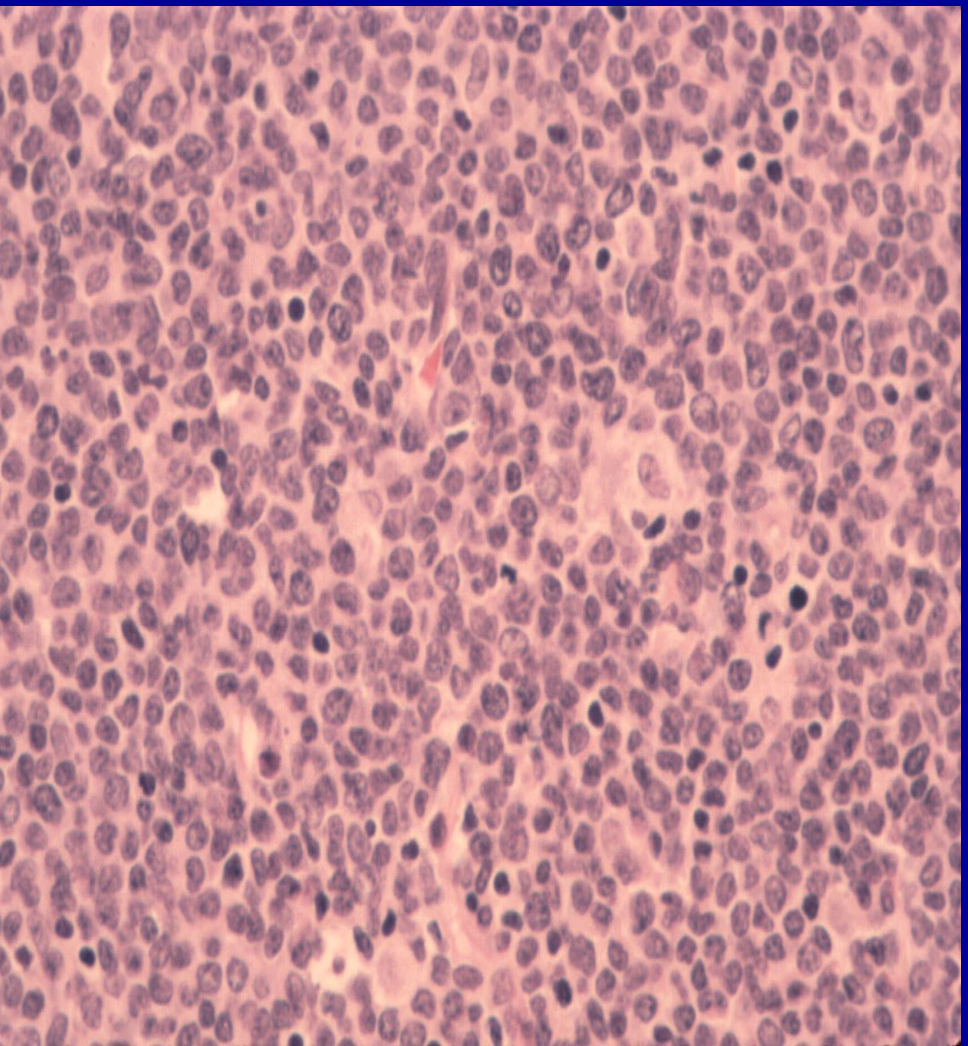


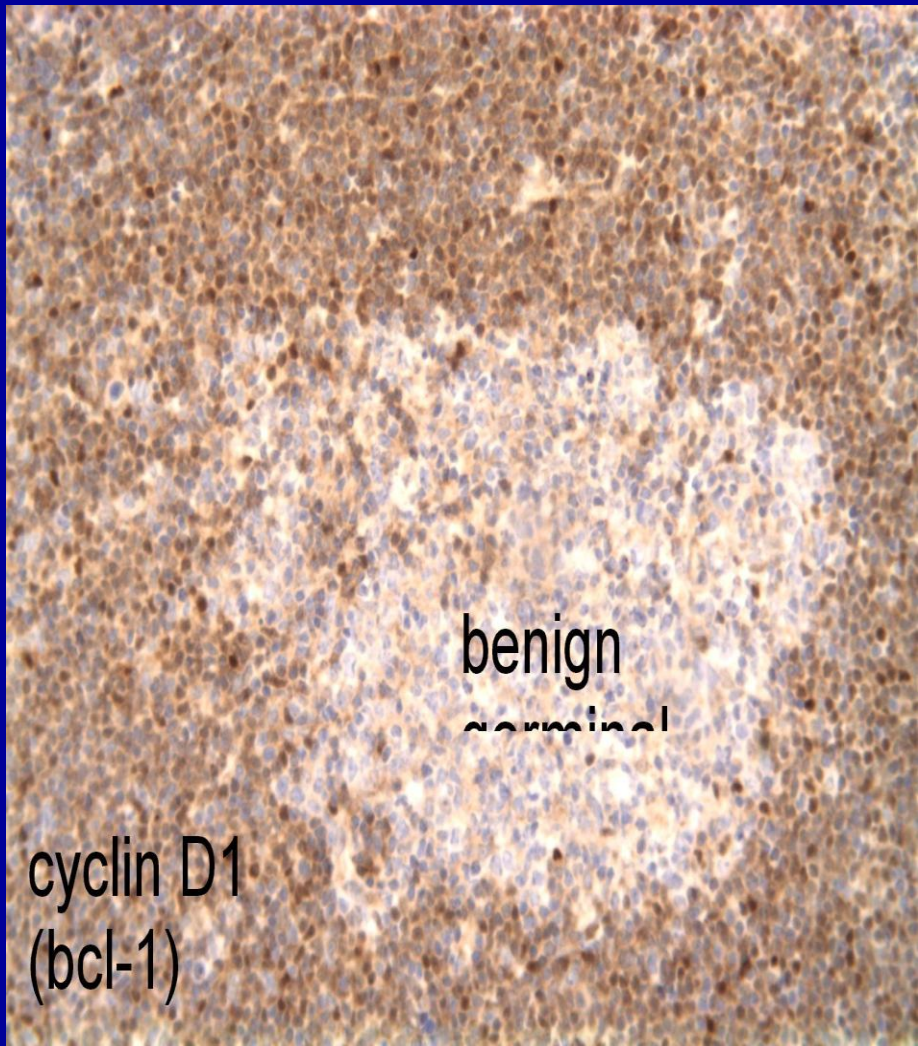
CD20+ (B cell)
CD5+ (T cell)
CD23 -
Bcl-1+

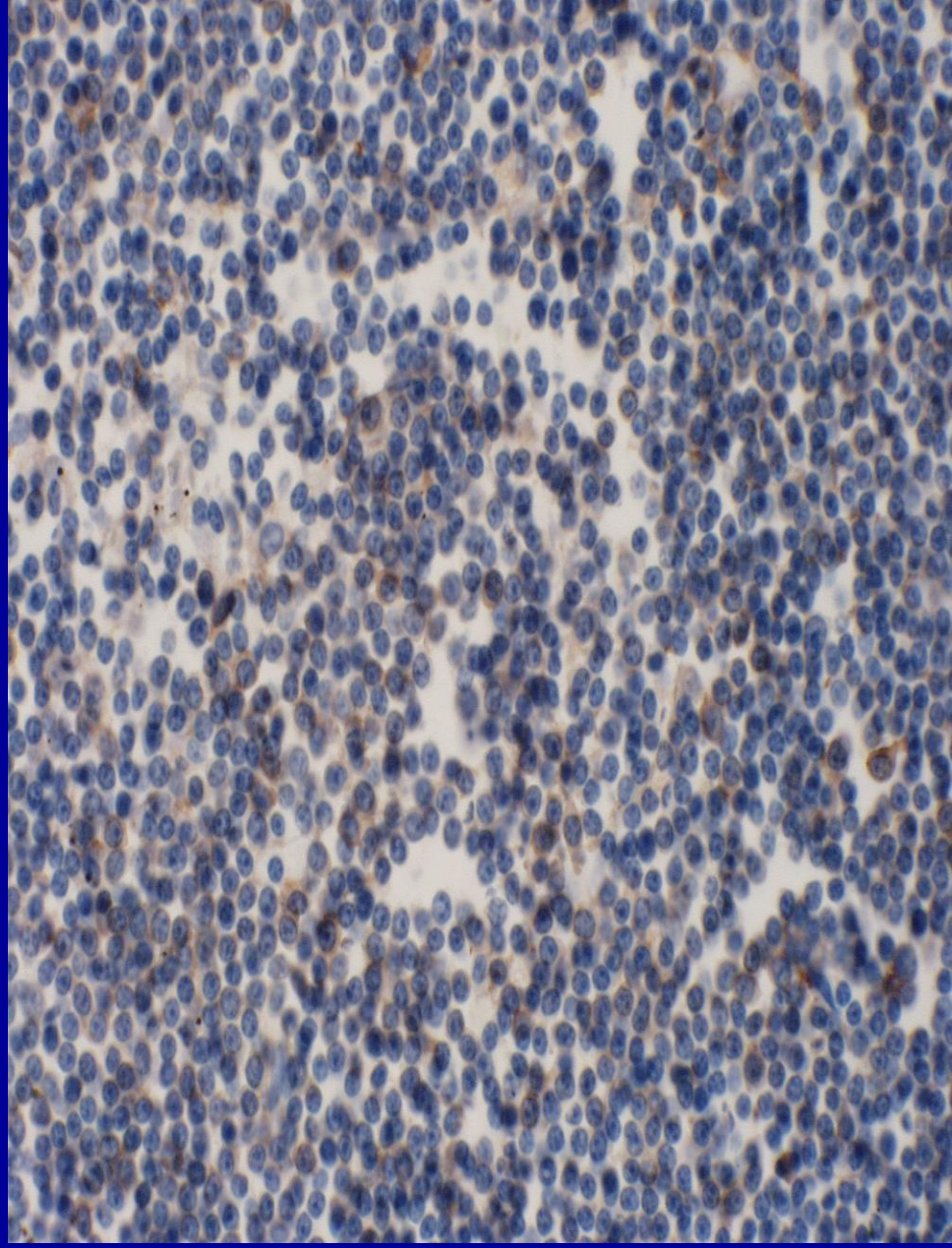
Mantle cells



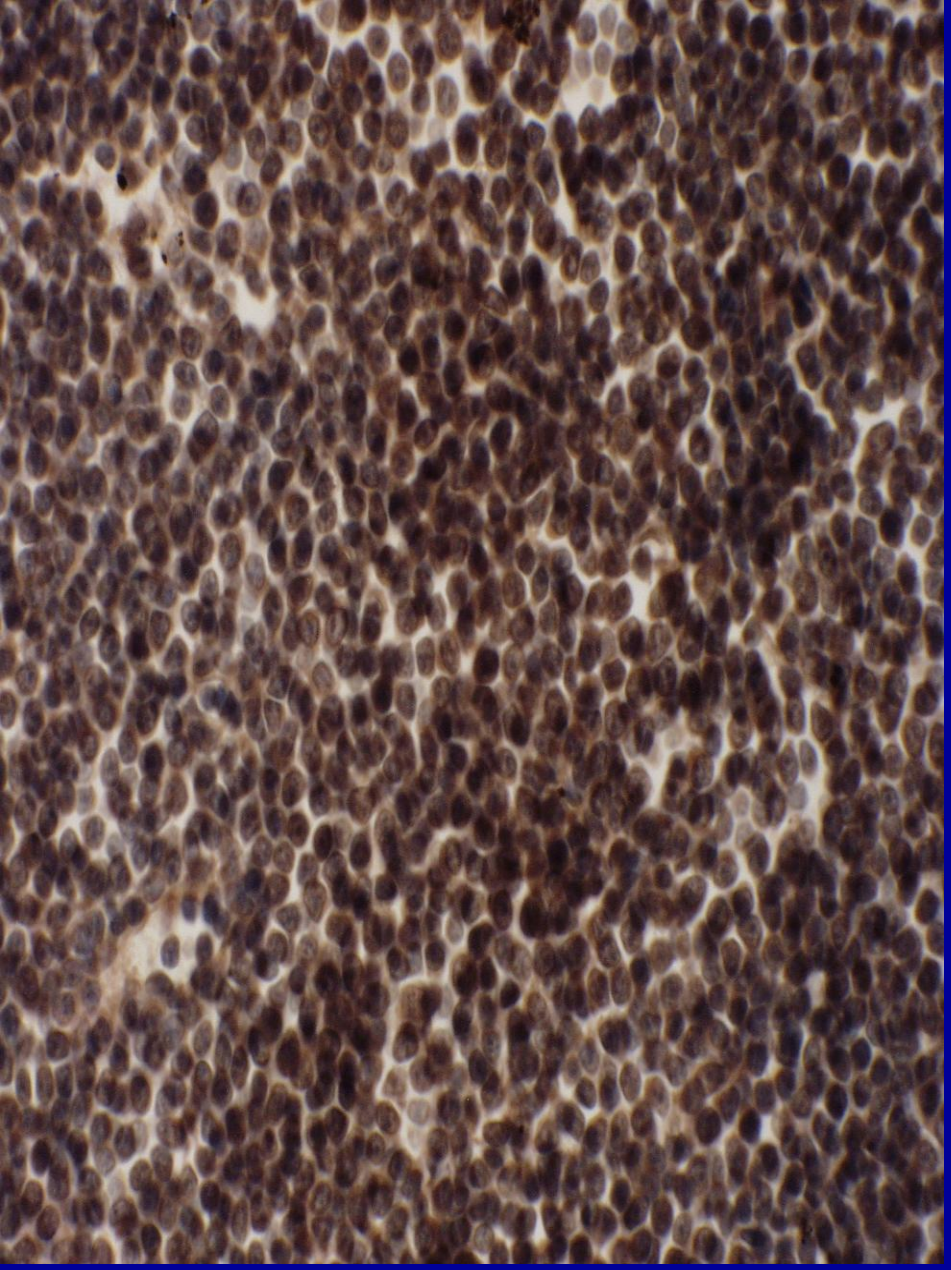
Diffuse pattern-in mantle cell lymphoma -blastic variant

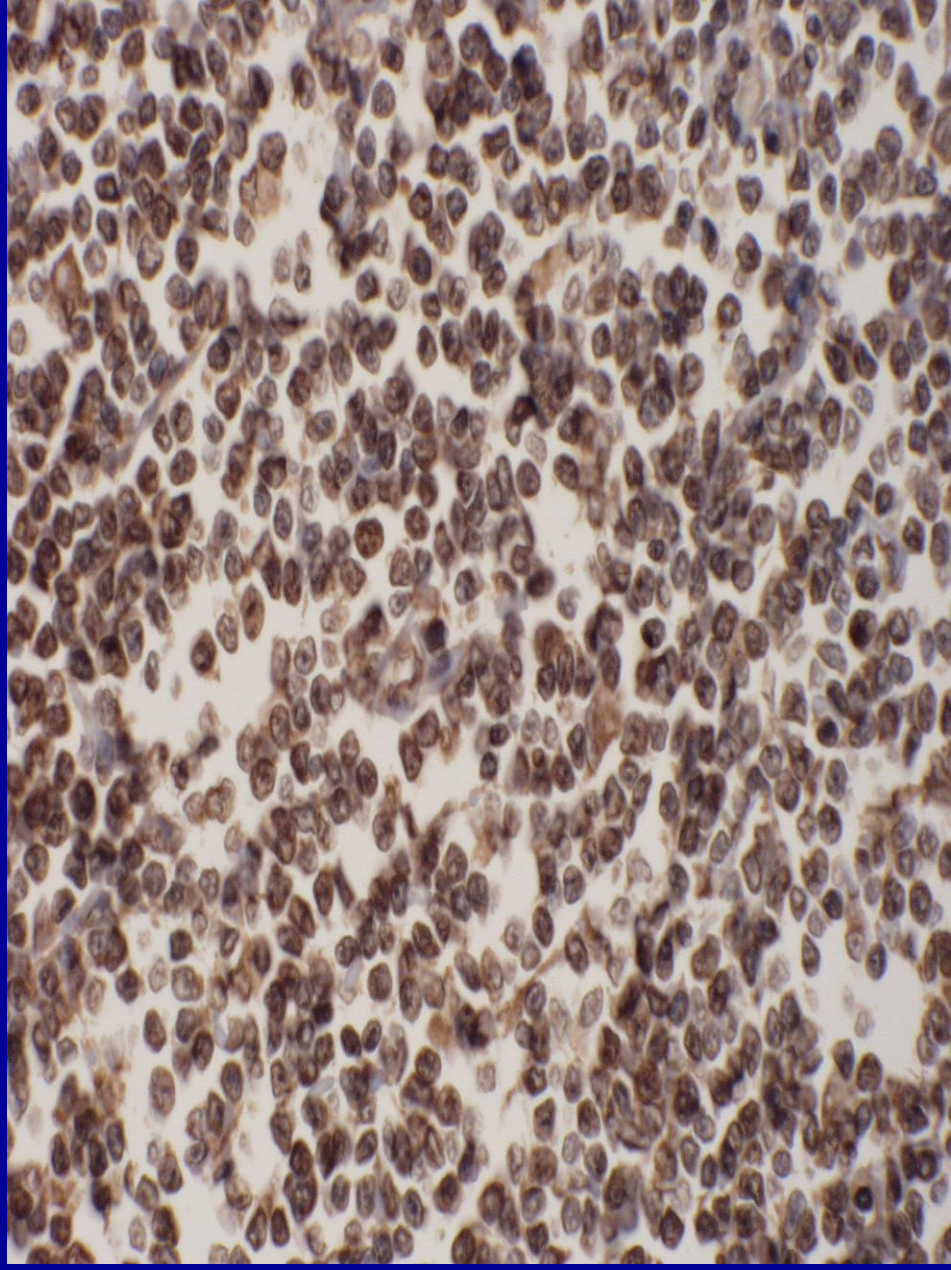




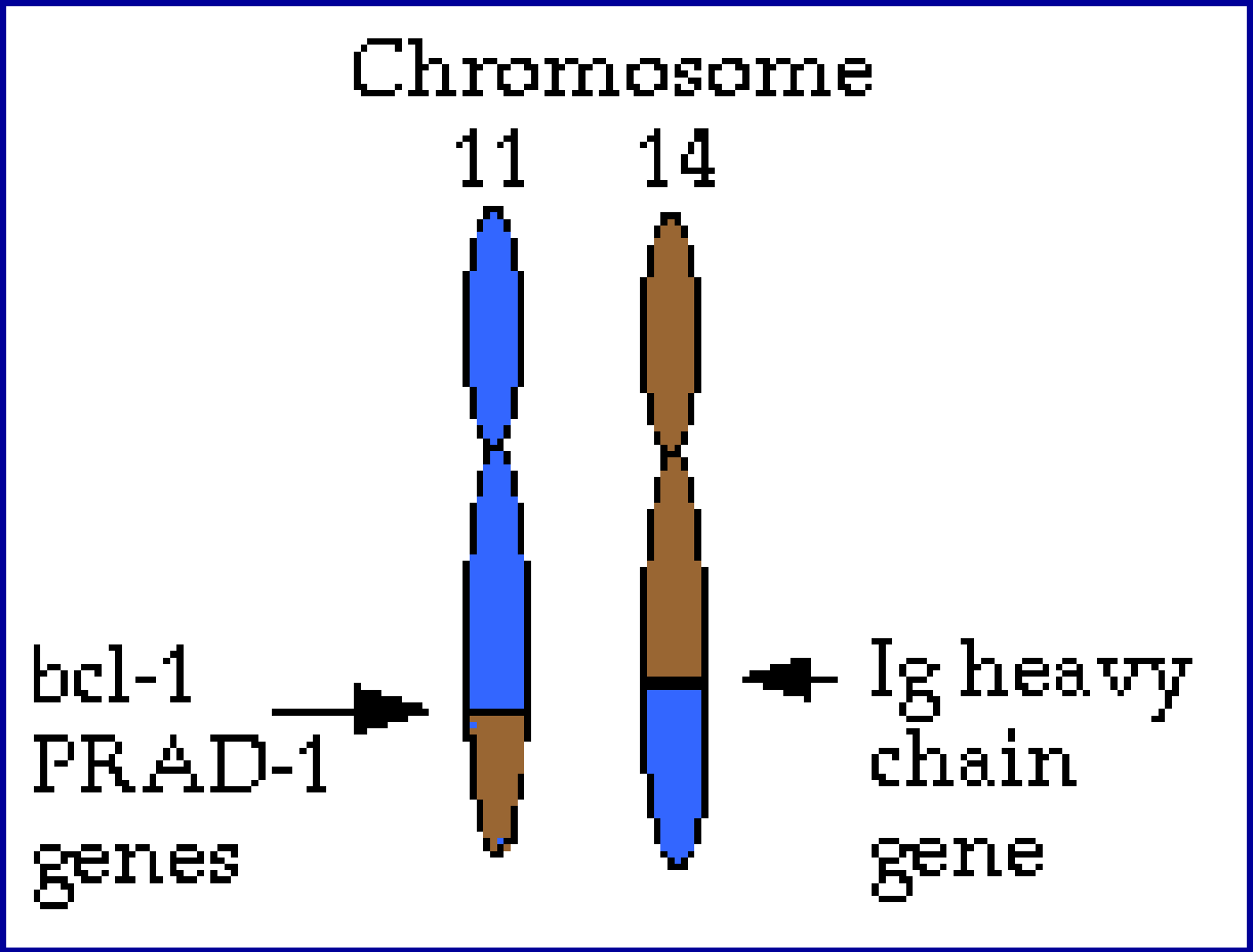


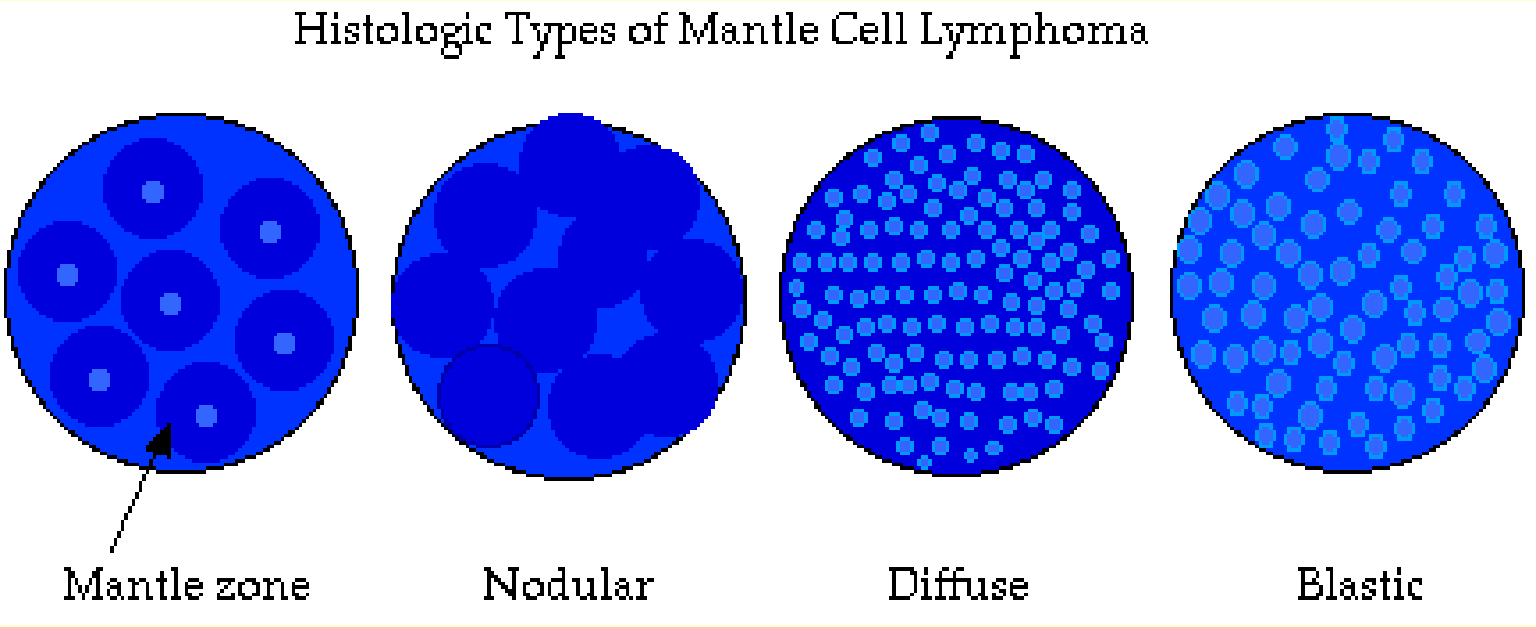
CD20(B cell)-Ctrl/Patient





Mantle cell lymphoma Cyclin D1- Ctrl / Patient

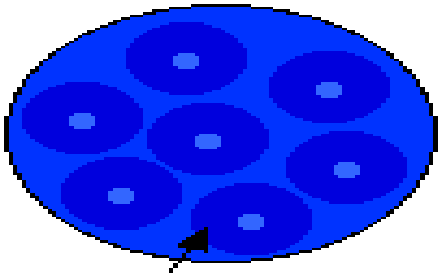

Chromosome
11
14
bcl-1
PRAD-1
genes
Ig heavy
chain
gene



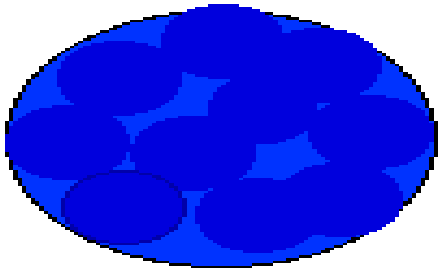
BECAUSE OF THE VARIOUS HISTOLOGIC FACETS OF MANTLE CELL LYMPHOMA, IN THE ERA OF PURE MORPHOLOGY, IT BECAME A GREAT MIMIC OF OTHER ENTITIES.

- IT MIMICKED SMALL LYMPHOCYTIC OR FOLLICULAR SMALL CLEAVED OR DIFFUSE SMALL CLEAVED OR EVEN LYMPHOBLASTIC

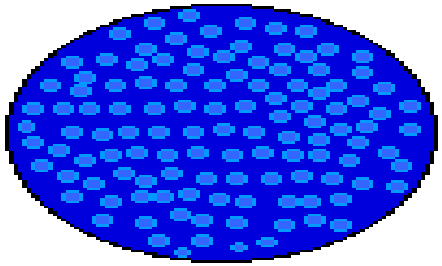
Histologic Types of Mantle Cell Lymphoma



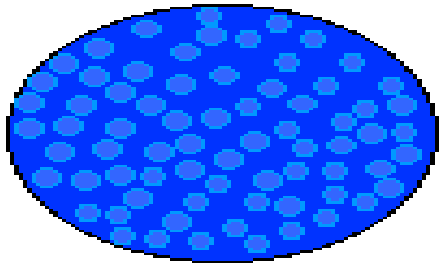
Mantle zone



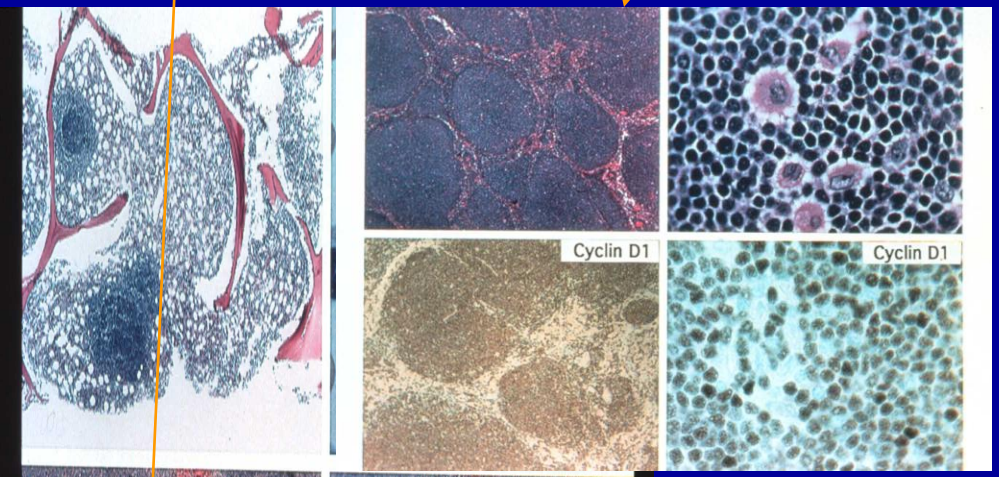
Nodular

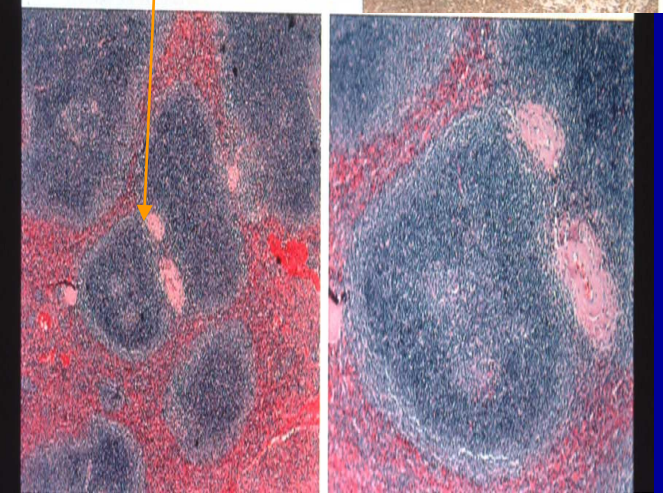


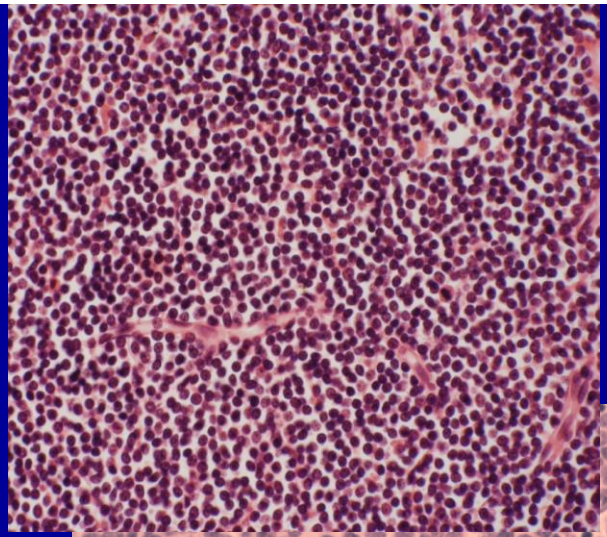
Diffuse

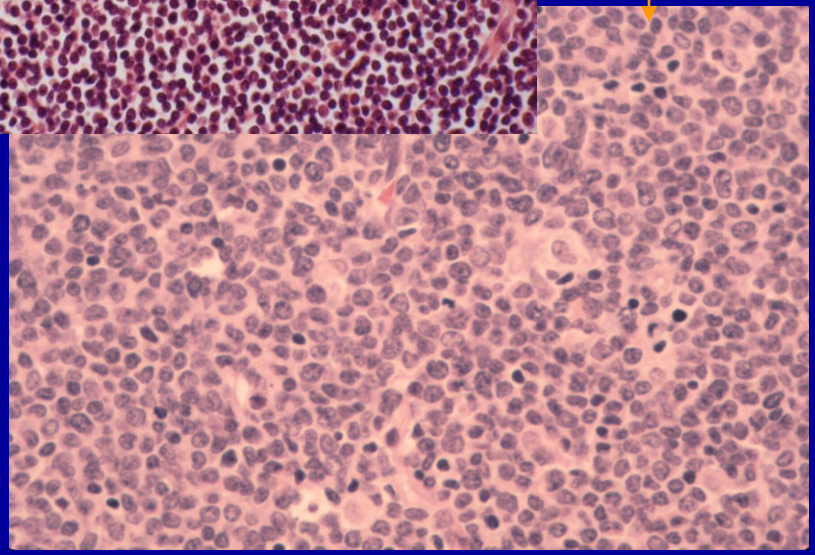


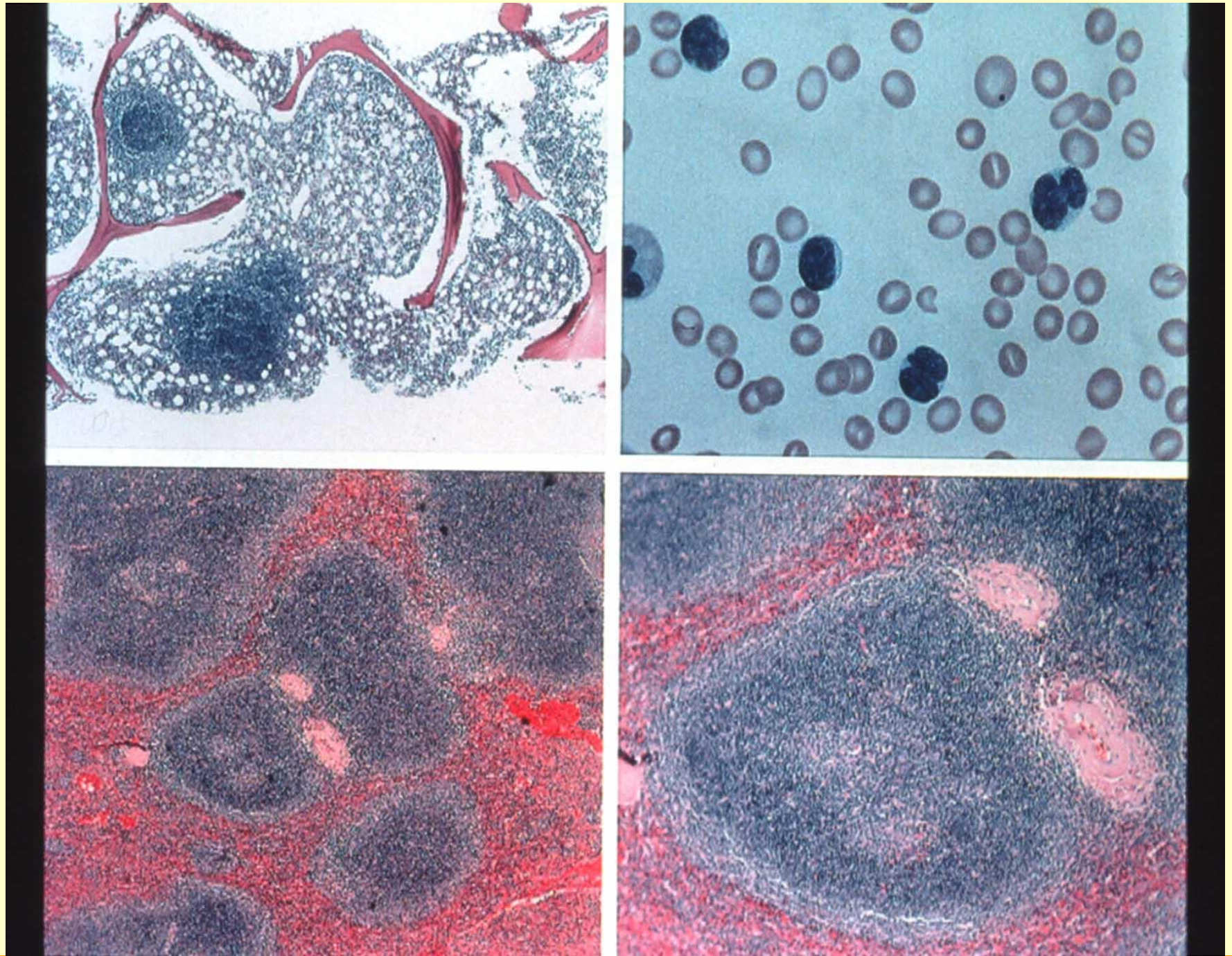
Blastic







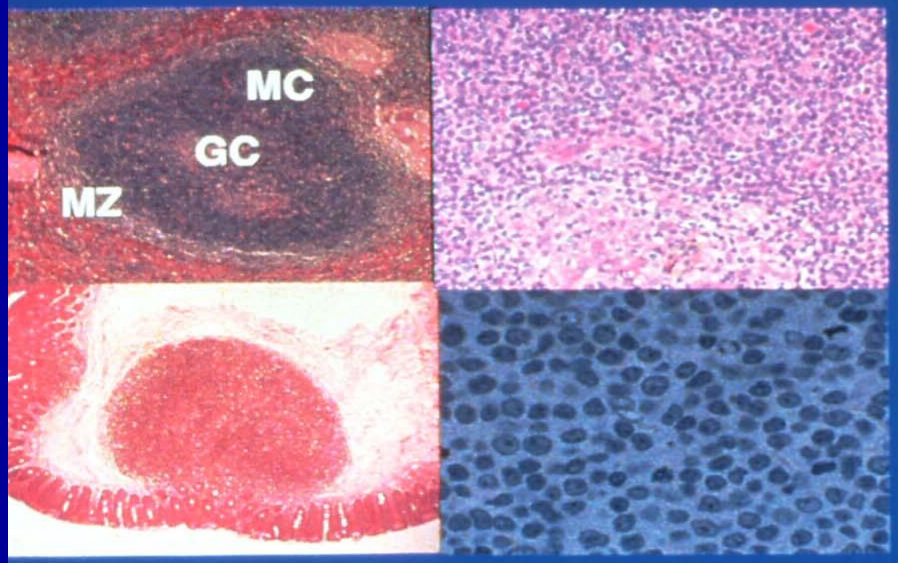


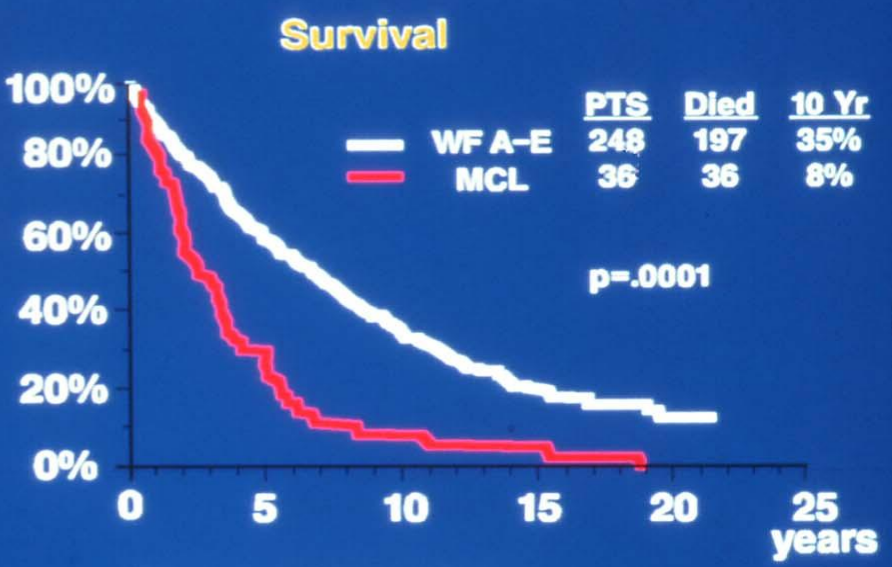


Clinico-pathologic summary

SWOG 8819 Clinicopathologic Definition of Mantle Cell Lymphoma

Consensus Dx: Banks, Grogan, Nathwani. Blood 85:1075, 1995

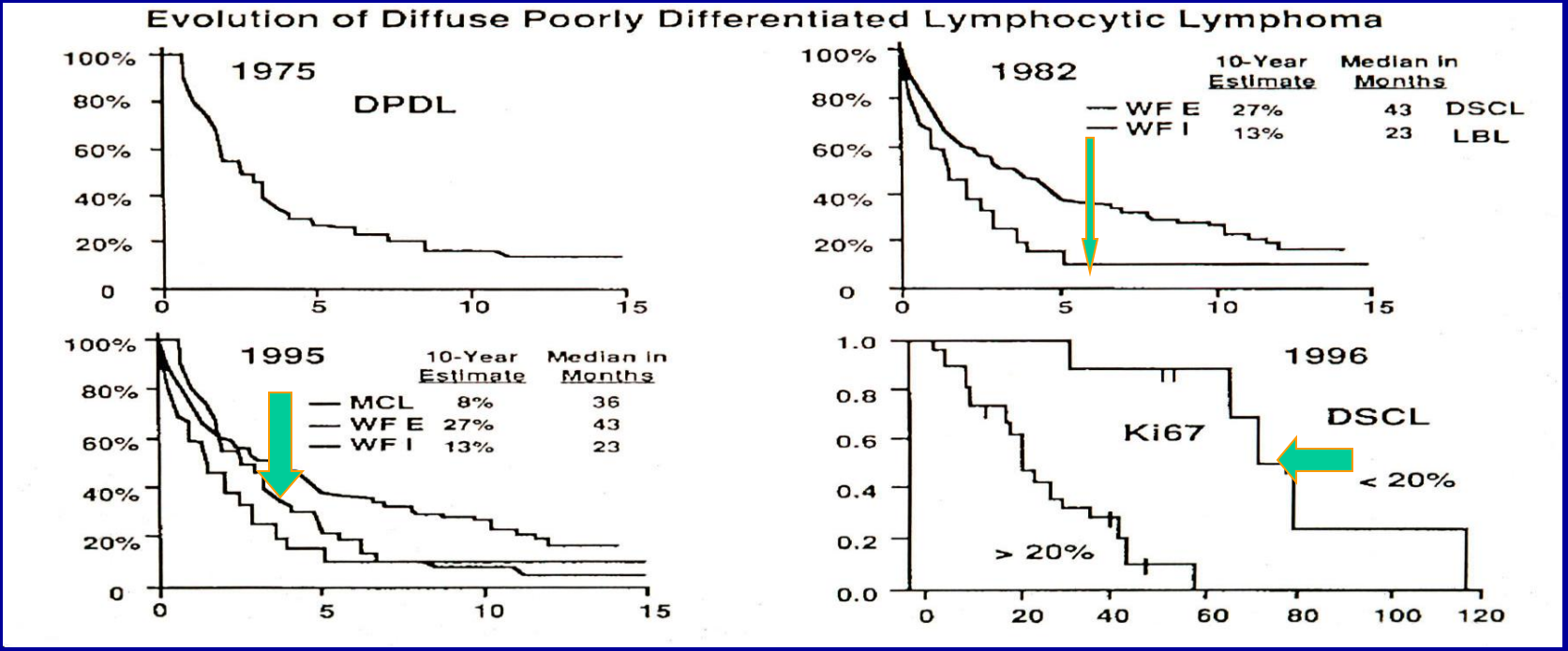




Clinical: Incidence 10%
- Median Age: 55 Male 81%
- PS>2 3% BM 53% GI 19%
- Survival: Median 3 yrs 10 yr: 8%

Immunogenotype:
- Monotypic Ig, Pan B^+
- $CD5^+$ 10^- 23^- 43^+
- Ki67 30% PRAD1 (cyclin D1)$^+$
- $bcl\text{–}1^+$ t(11,14)

Definition of MCL from the "mix"



DPDL-RAPPAPORT TERM CORRESPONDING TO DIFFUSE SMALL CLEAVE CELL LYMPHOMA (DSCL) OF THE WORKING FORMULATION

WF E= DIFFUSE SMALL CLEAVED

WF I= LYMPHOBLASTIC

MCL=MANTLE CELL LYMPHOMA

KI-67 PROLIFERATIVE MARKER AS A PROGNOSTIC MARKER INDEPENDENT OF MORPHOLOGY

CD19-KAPPA

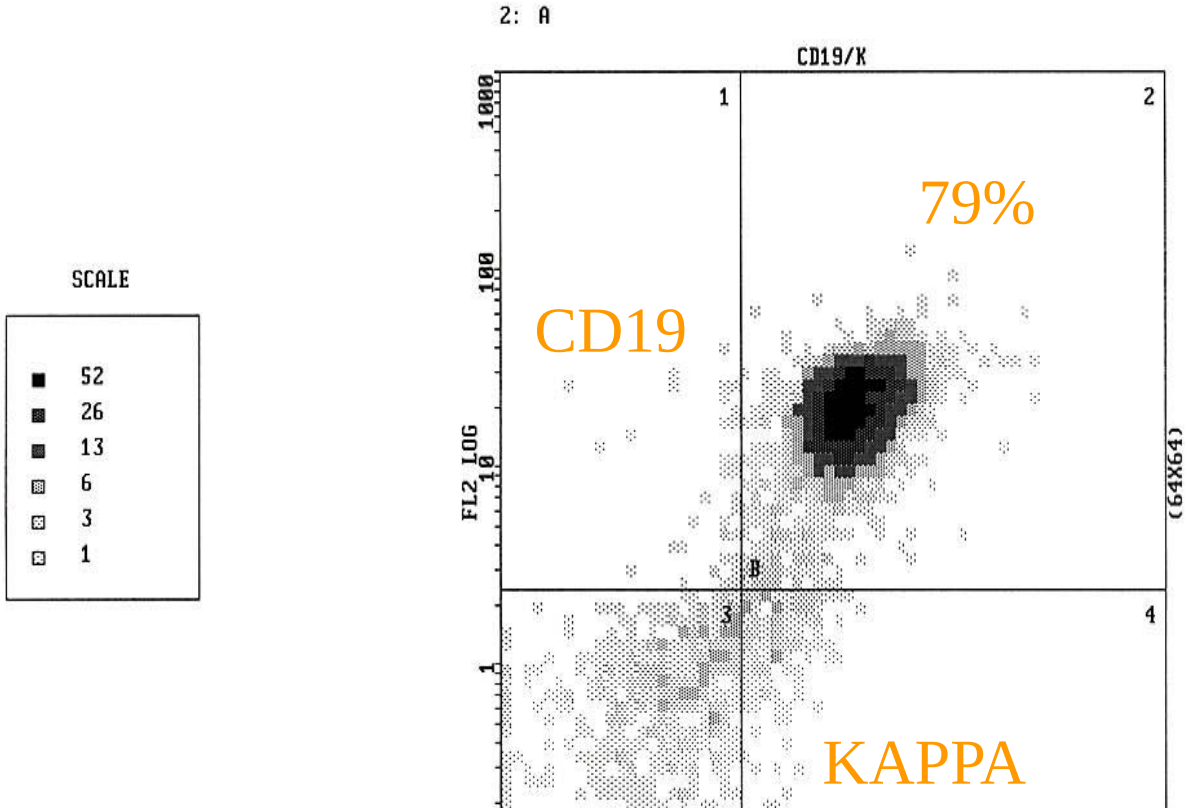
HEALTH ALLIANCE LABORATORY SERVICES

COULTER(R) EPICS(R) Listmode Replay Flow Cytometry Report
D:\NOV96\NODE\A0057128.LMD, XL W24191, Run time protocol

26Nov96 17:19:47
CD19/K
A0057128

OP ID: RAH

20 seconds, 5191 events
Stop Hist 2, 5000 events



CD20+CD5+

HEALTH ALLIANCE LABORATORY SERVICES

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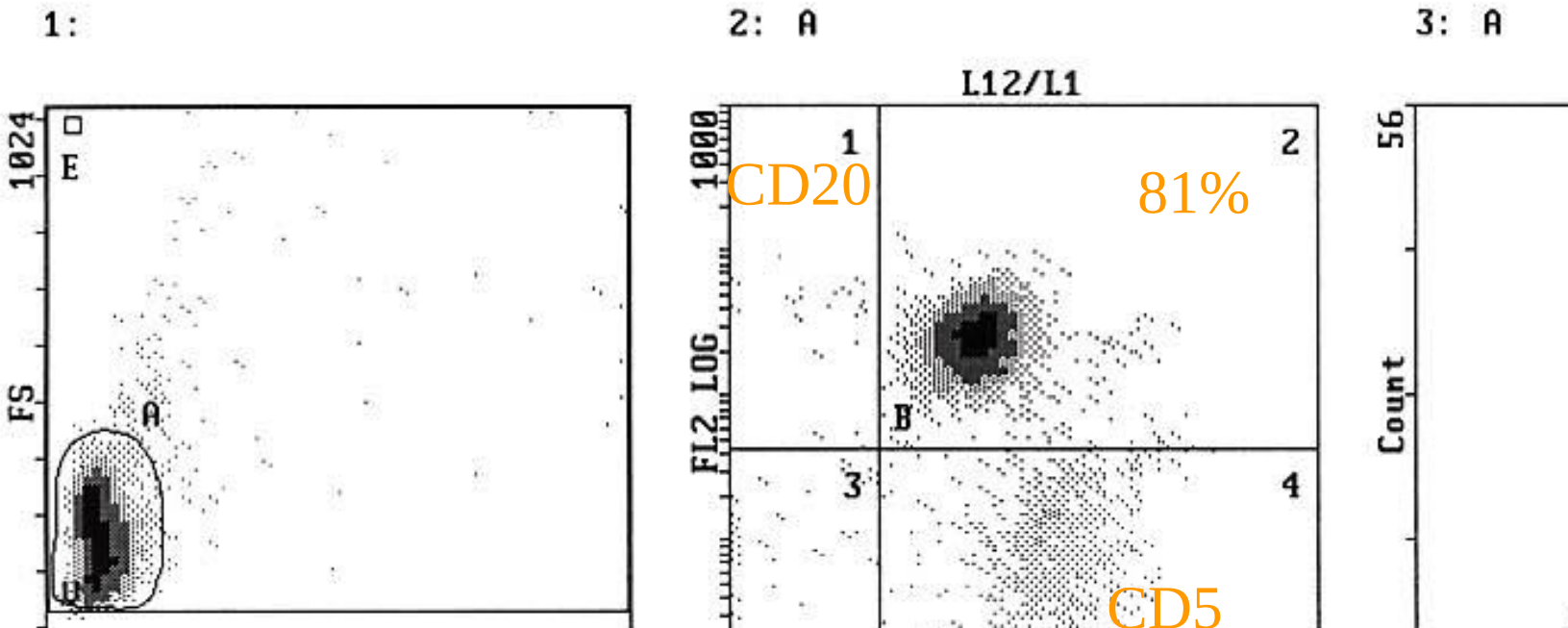

CD19+ LAMBDA -

HEALTH ALLIANCE LABORATORY SERVICES

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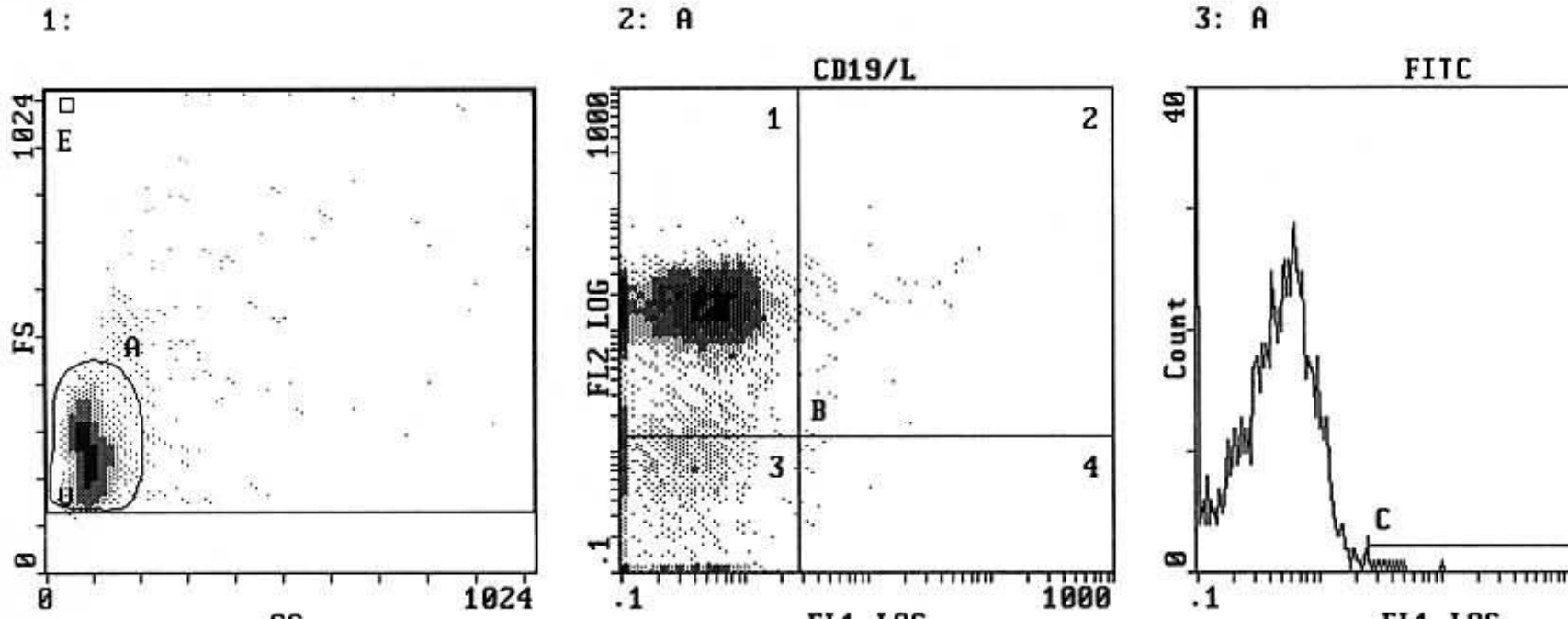

CD20+, CD23 -

HEALTH ALLIANCE LABORATORY SERVICES

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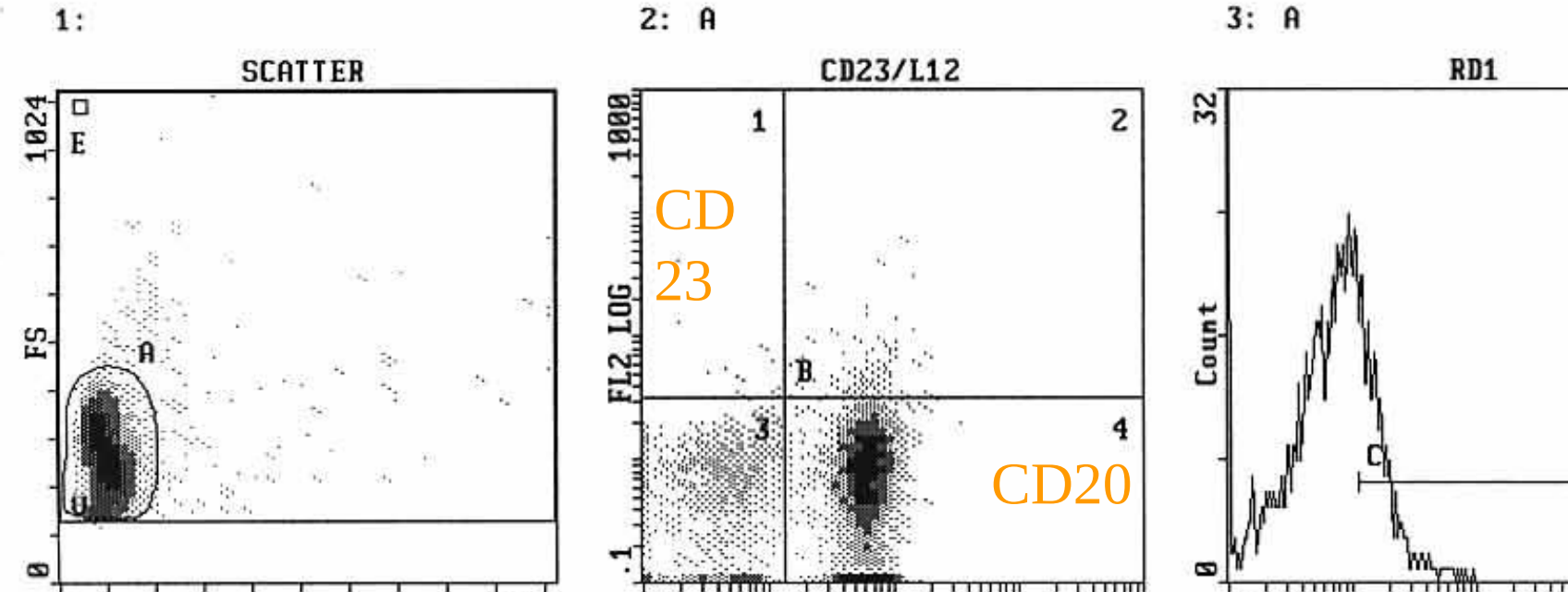
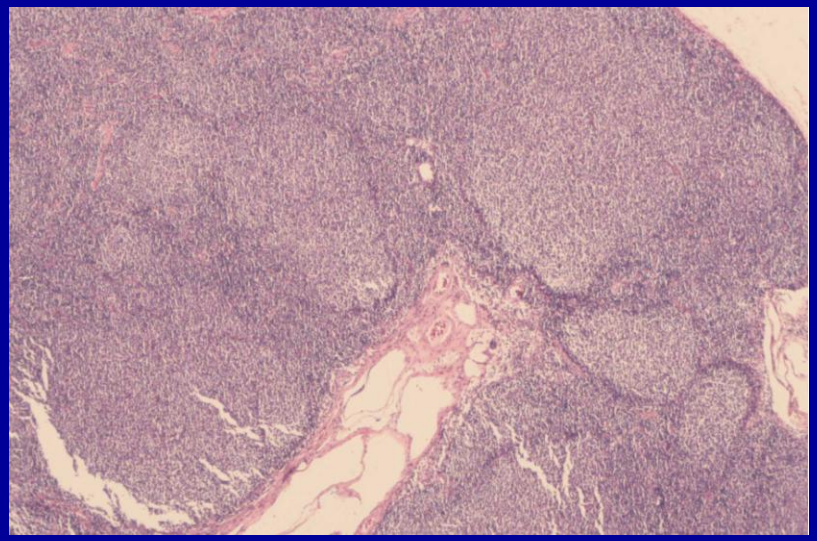
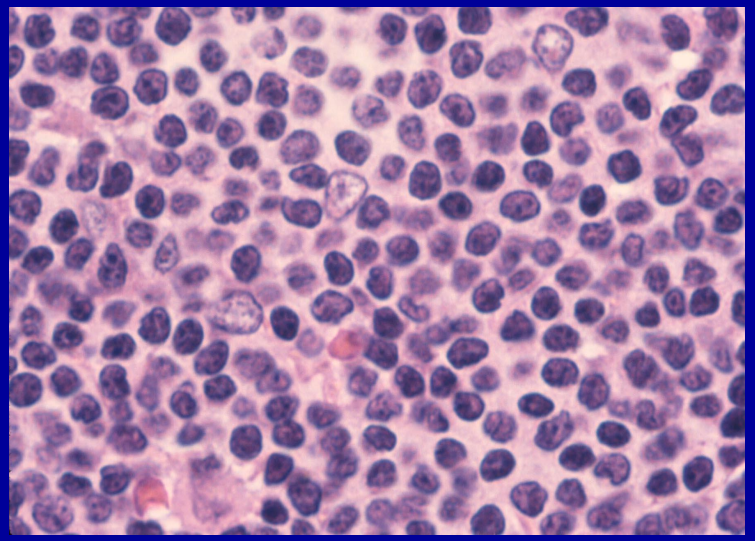
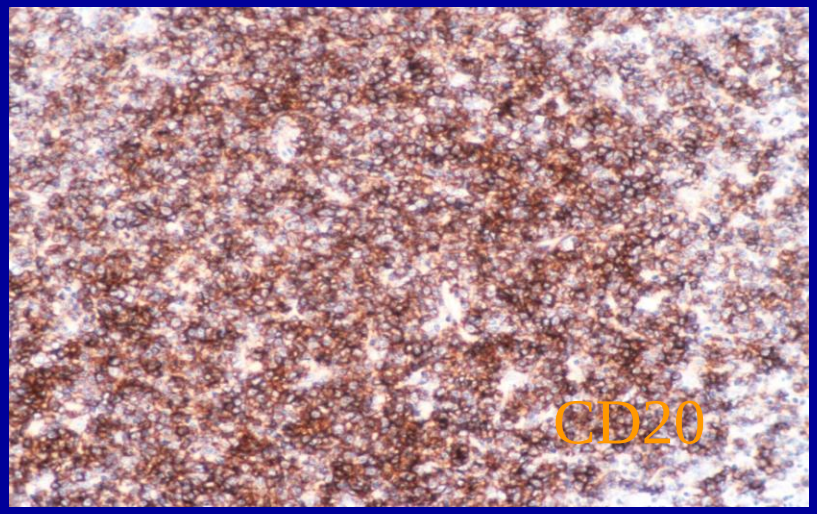
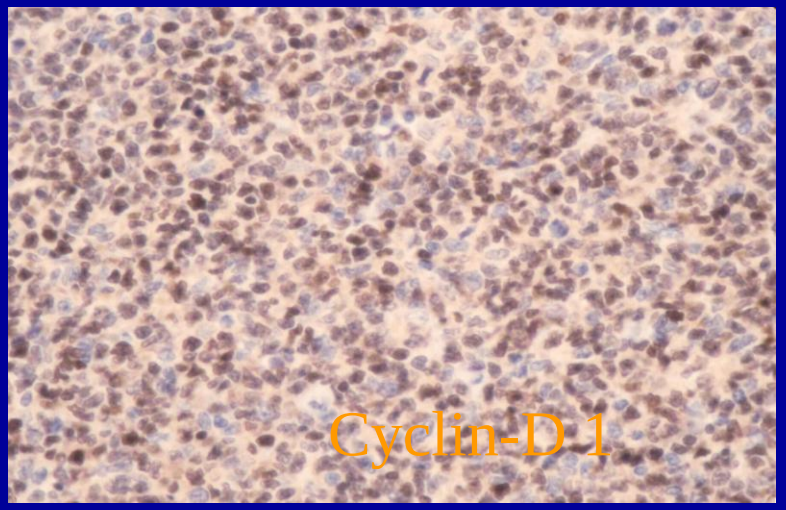


NODULAR FORM OF MCL, CD20+, CYCLIN d1+

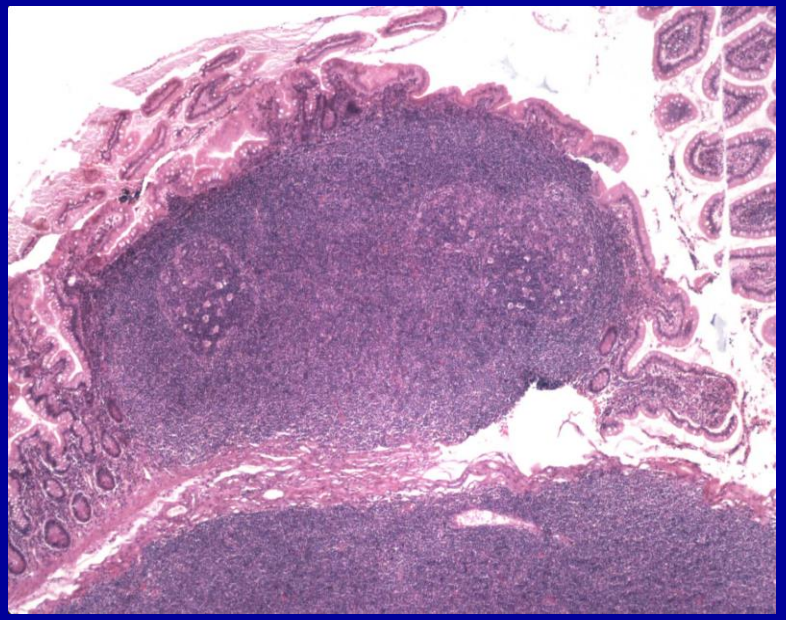


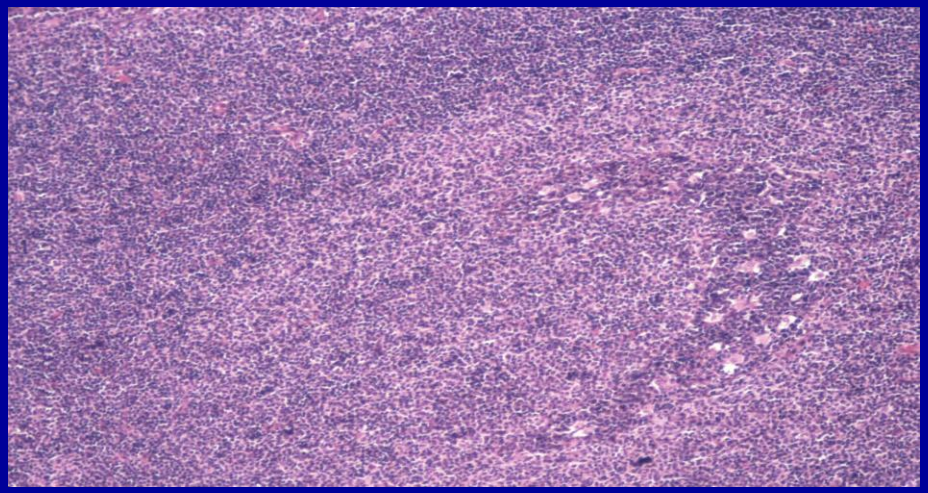






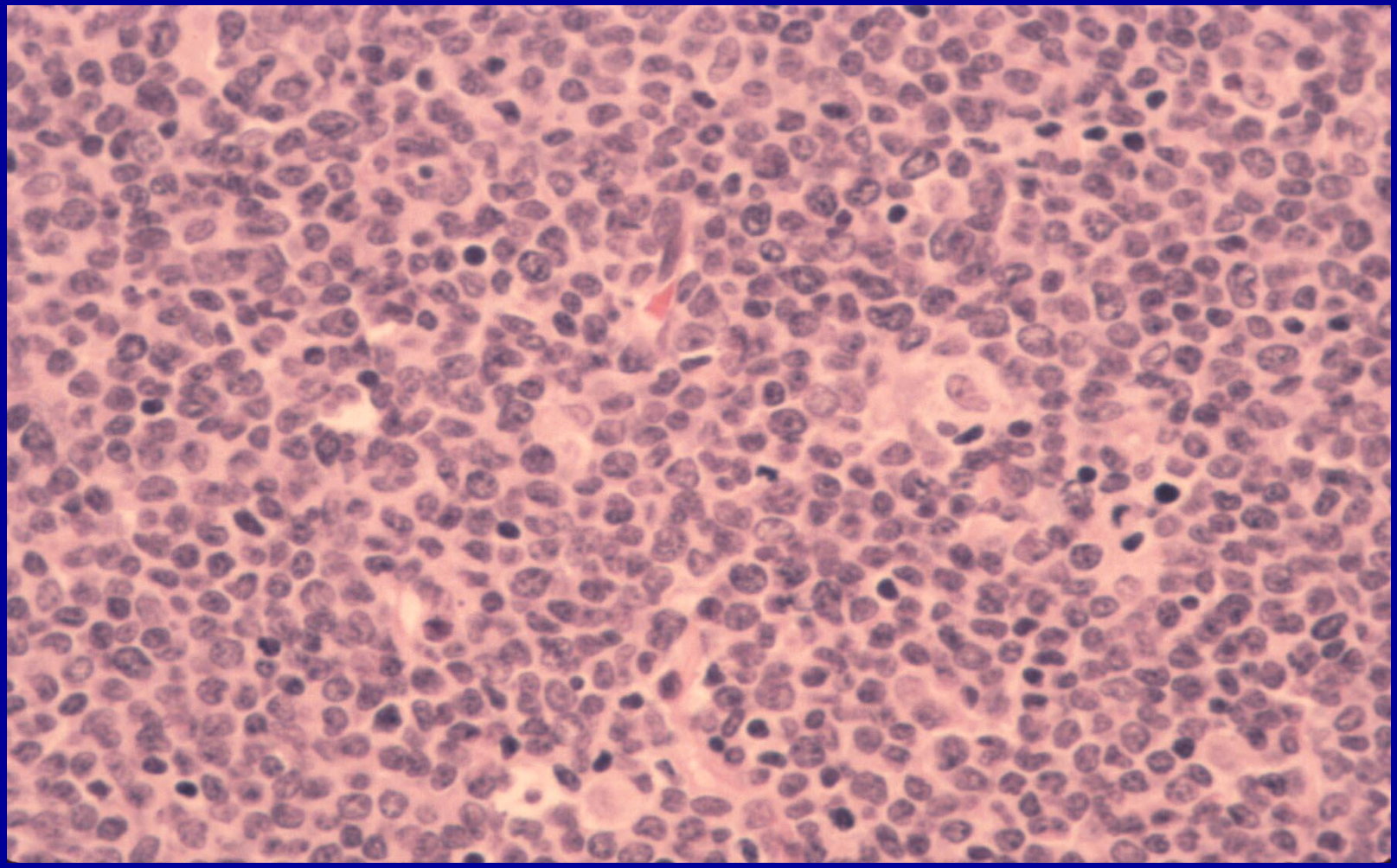
EXTRANODAL MCL -LYMPHOMATOUS POLYPOSIS



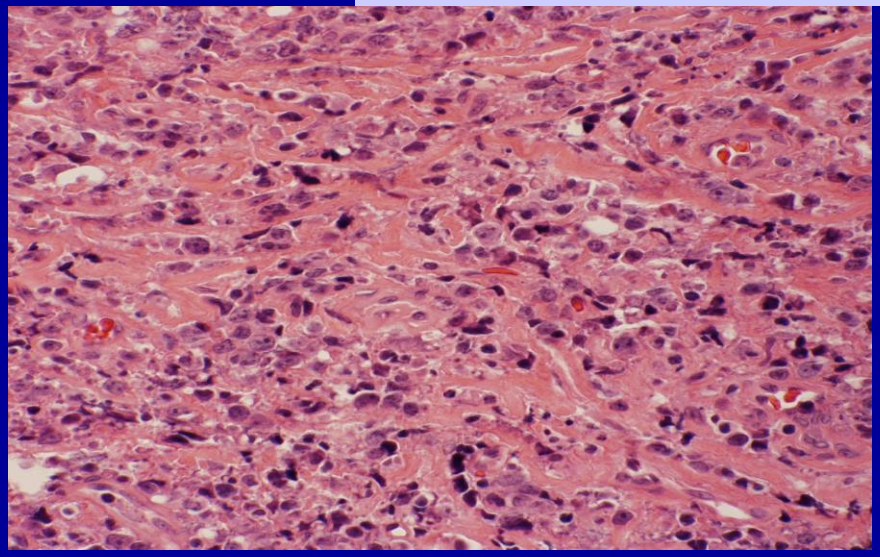


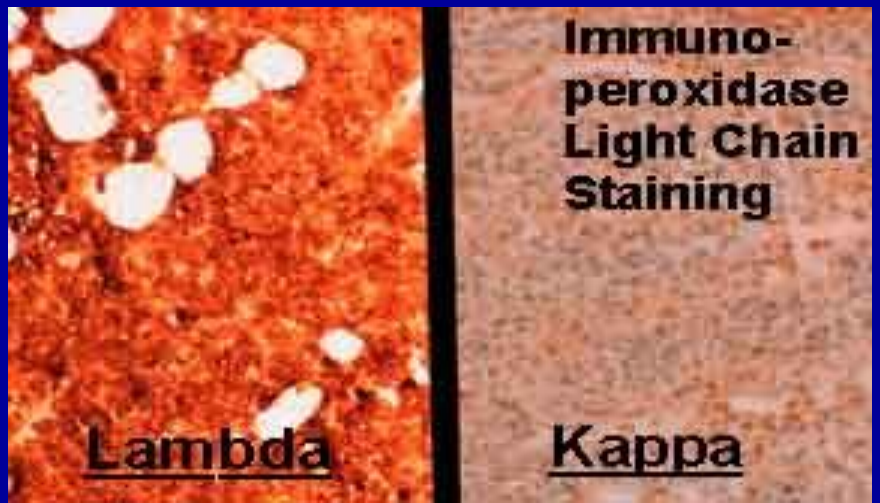
CD20+ (B cell)
CD5+ (T cell)
CD23 -
Cyclin D1+

Blastic variant



Diffuse Large B-Cell Lymphomas (DLBCL)





- Heterogeneous
- comprise the majority of diffuse aggressive lymphomas in both adults and children
- Extranodal location common
- Reactive components may be prominent
- Responds well to chemotherapy
- Usually a CD19,CD20, CD79a+ monoclonal B-cell
- lower incidence of BM involvement

WHO Diffuse Large B-cell lymphoma- 6 Morphologic Variants and 3 Clinical subtypes

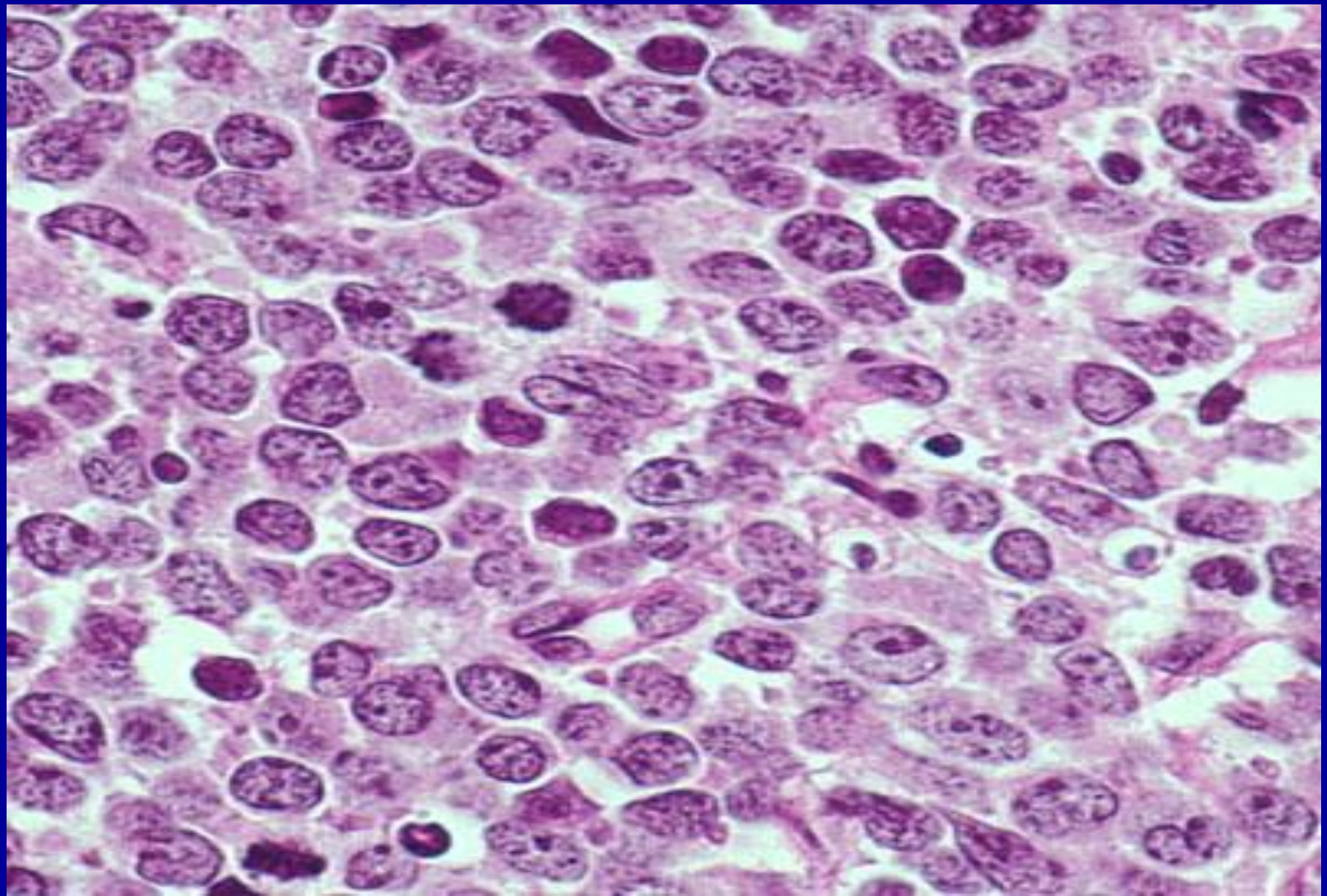
Morphologic Variants

- **Centroblastic**
- **Immunoblastic**
  - **T-cell histiocyte-rich**
- **Lymphomatoid granulomatosis type**
- **Anaplastic**
- **Plasmablastic**

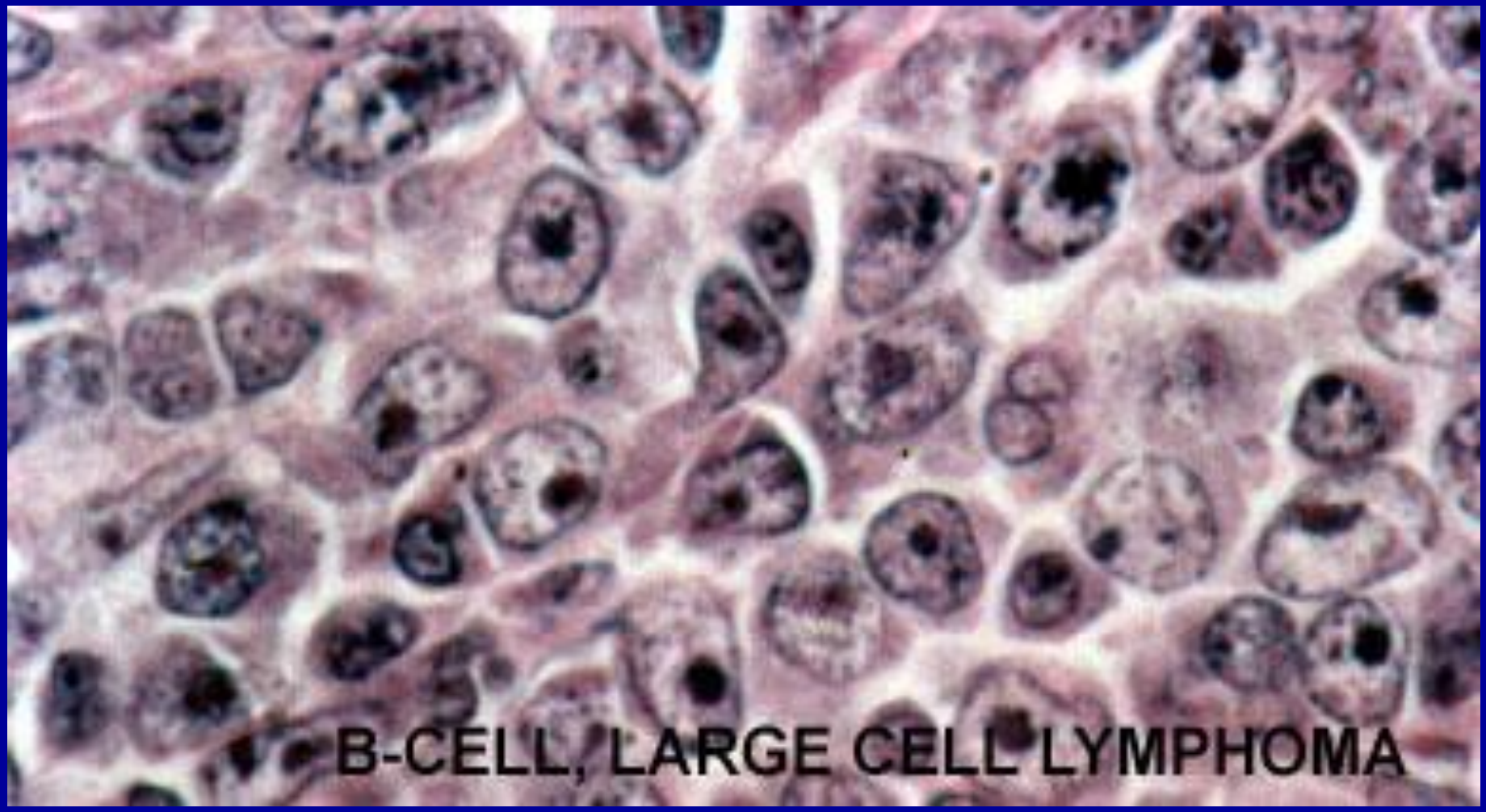
Clinical Subtypes

- **Mediastinal (thymic)**
- **Primary effusion lymphoma**
- **Intravascular**

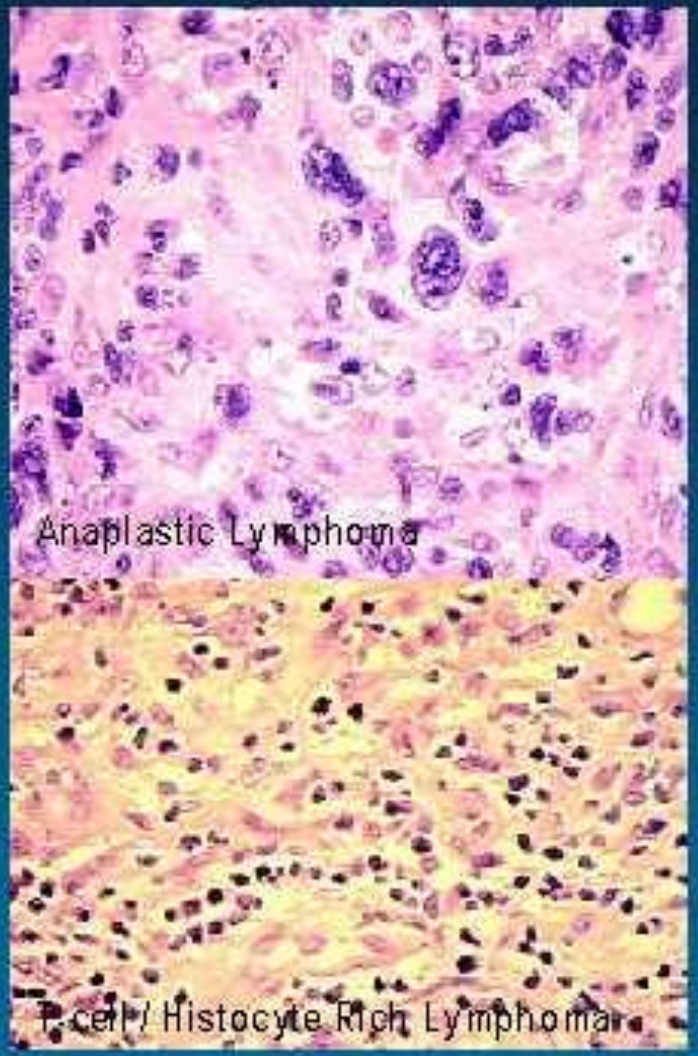
CENTROBLASTIC



Immunoblastic variant



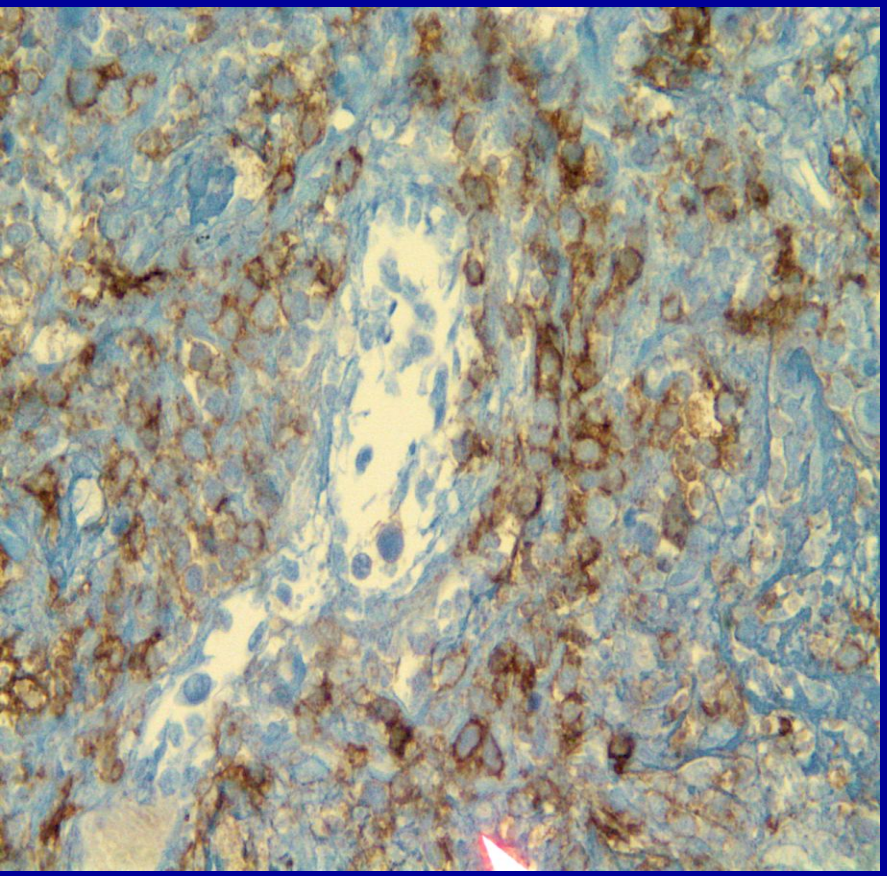
Diffuse Large Cell Lymphoma (B-cell)



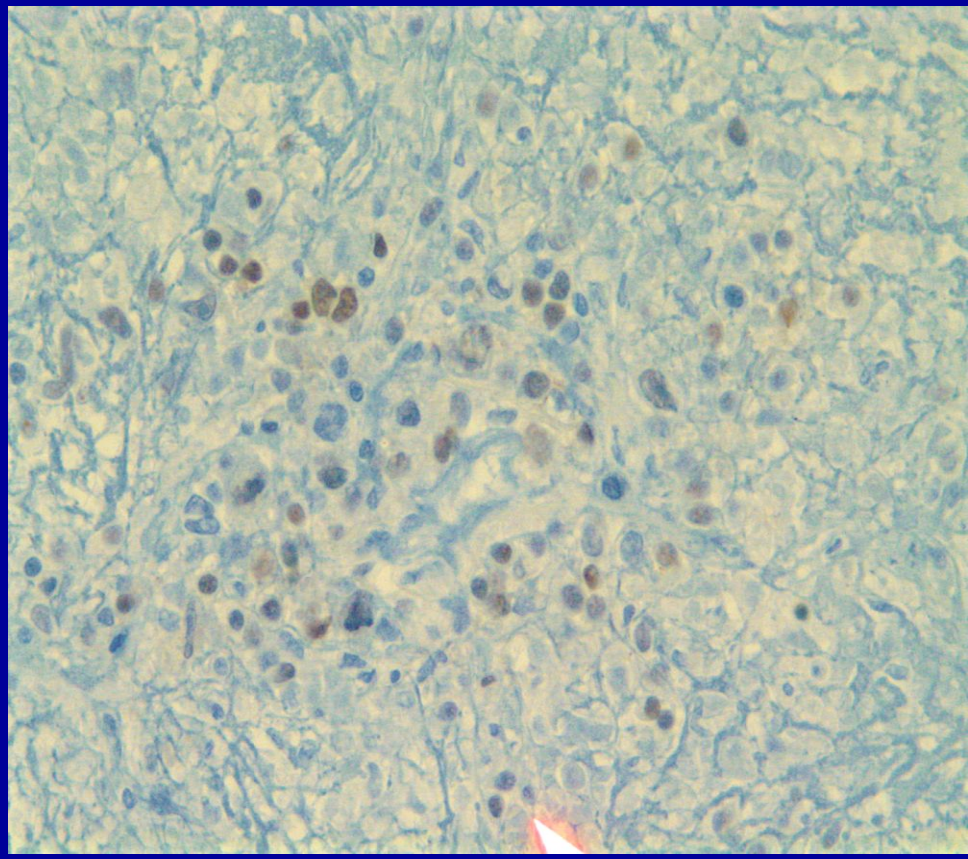
- Types
  - Anaplastic
  - T-cell / Histiocyte rich
  - DLBCL Intravascular lymphoma
- Immunophenotype
  - B-cell phenotype
  - CD19+, CD20+, CD22+, k or l+
  - CD3 and CD68 in the background

Lymphomatoid Granulomatosis may progress to a DLBCL (WHO

- Majority of cases are B-cell lymphomas
- Associated with Ebstein-Barr Virus
- Reactive small T-cells form majority of infiltrate

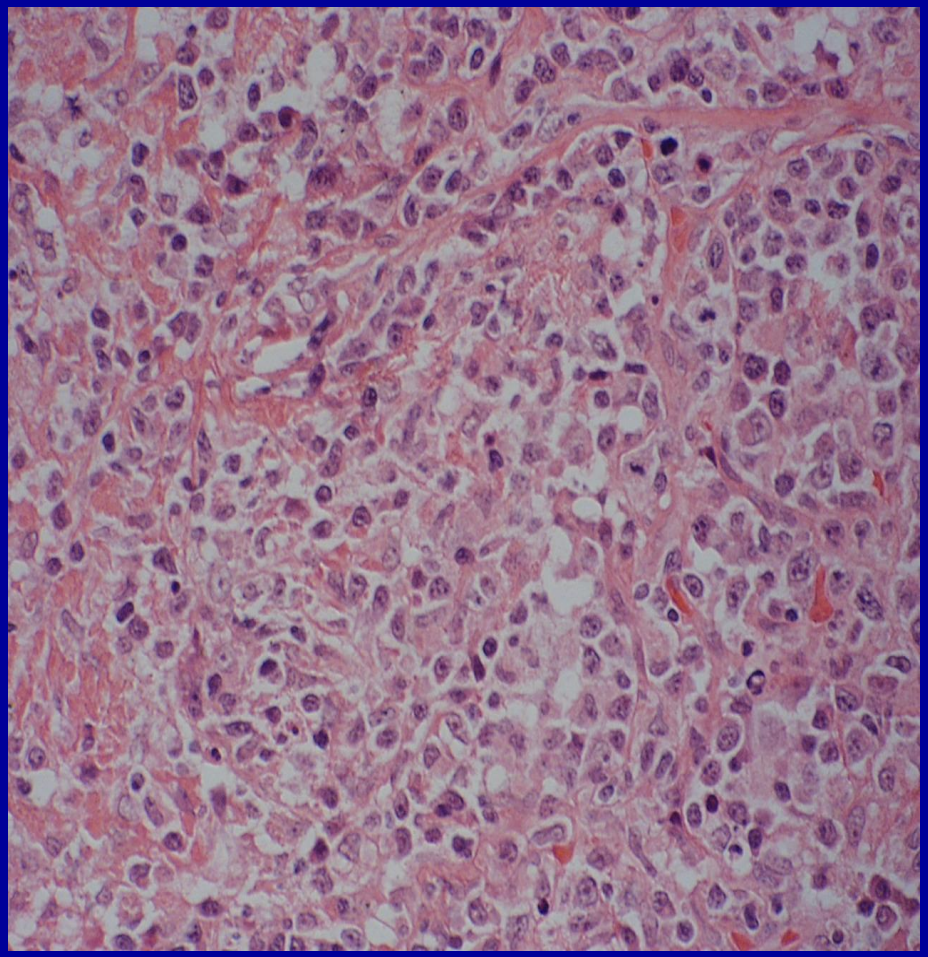


CD20+

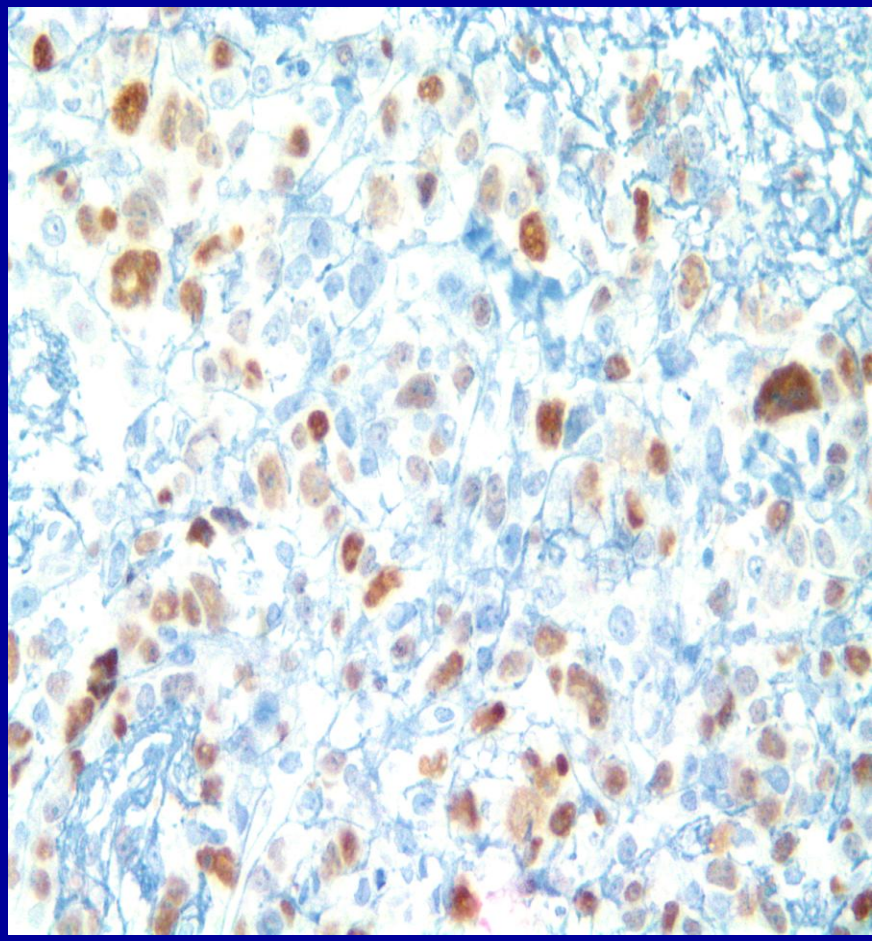


EBV+

Diffuse large B-cell lymphoma in LyG

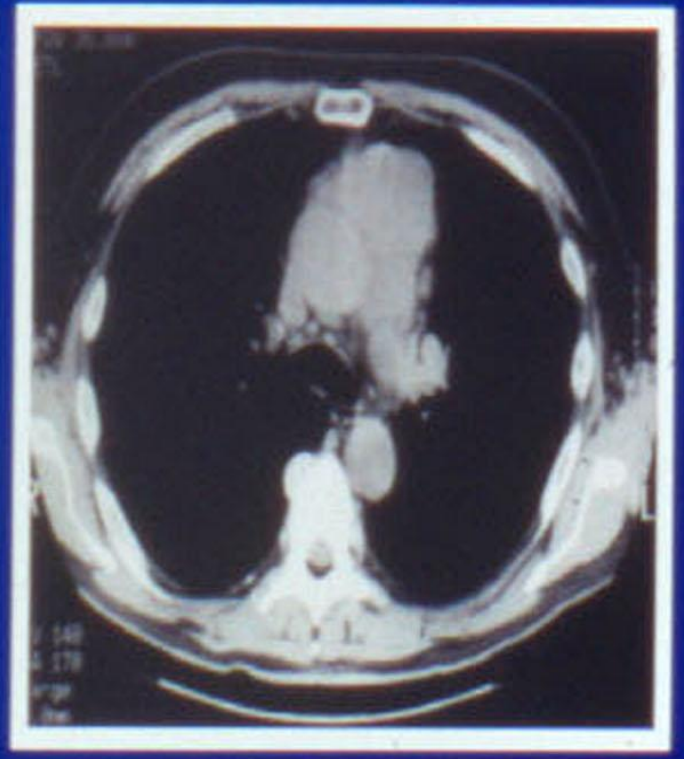


H and E



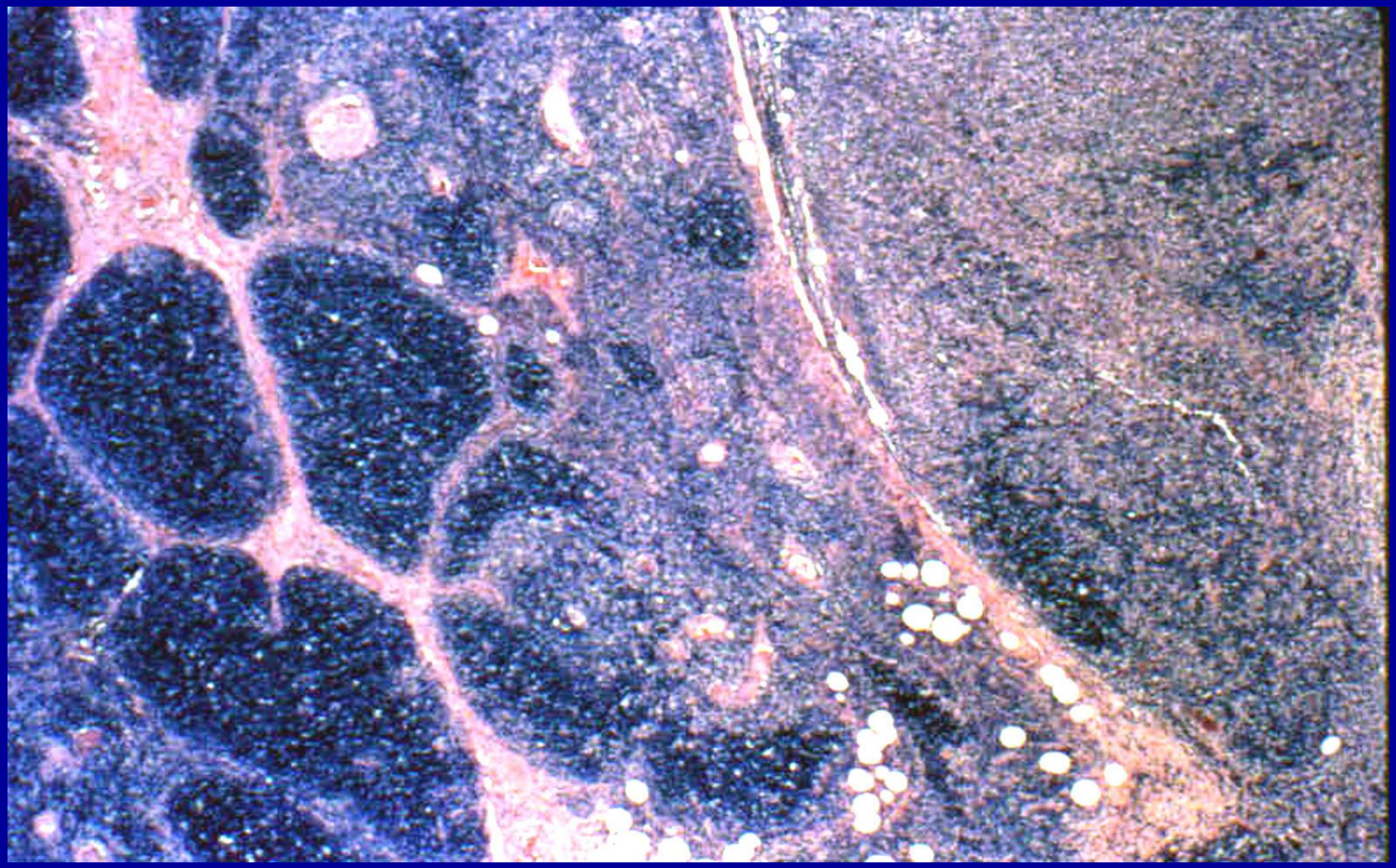
EB NA

Mediastinal Large cell lymphoma

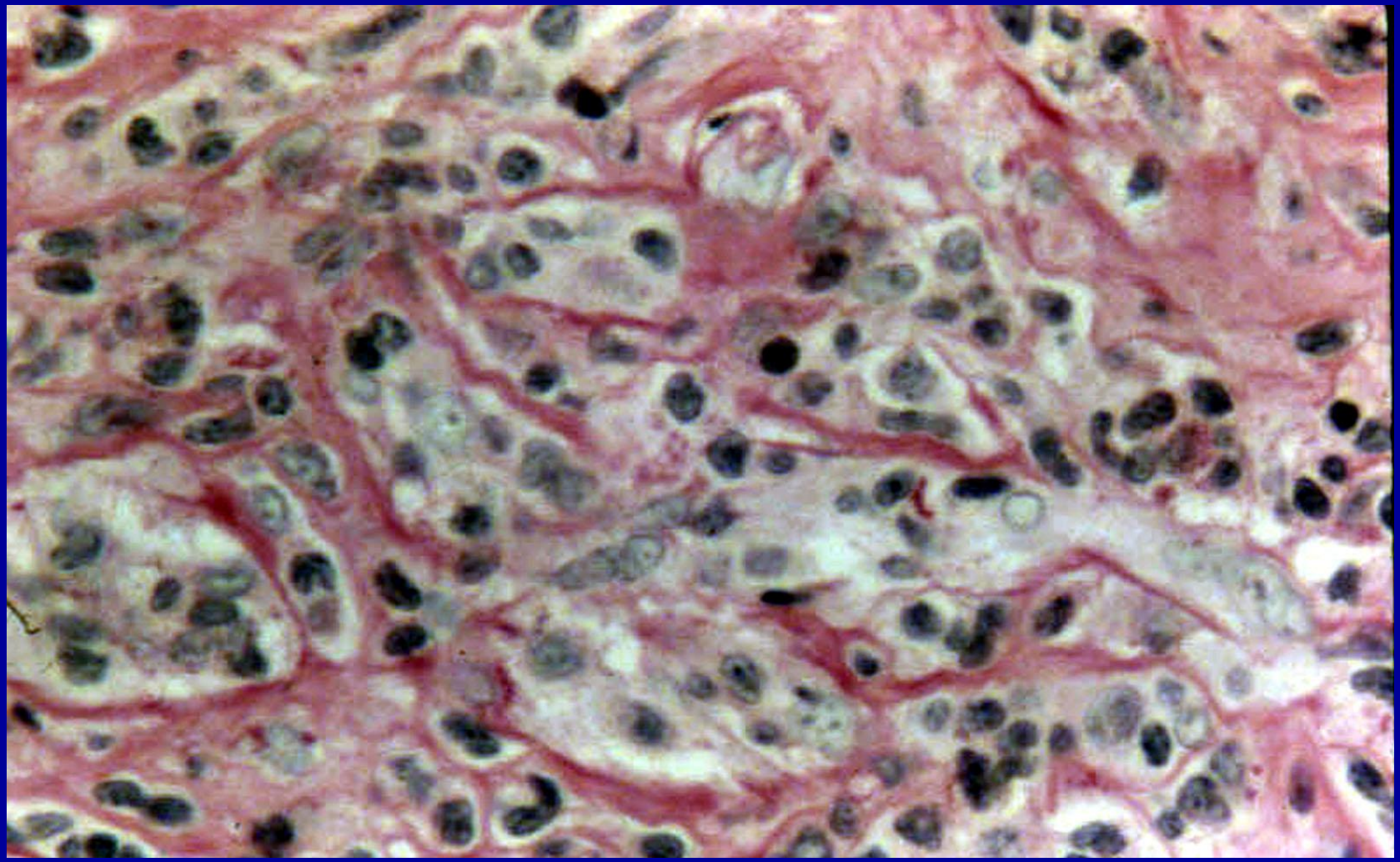


- bulging mediastinal mass, young female, large cell with or without sclerosis, locally aggressive, superior vena cava syndrome

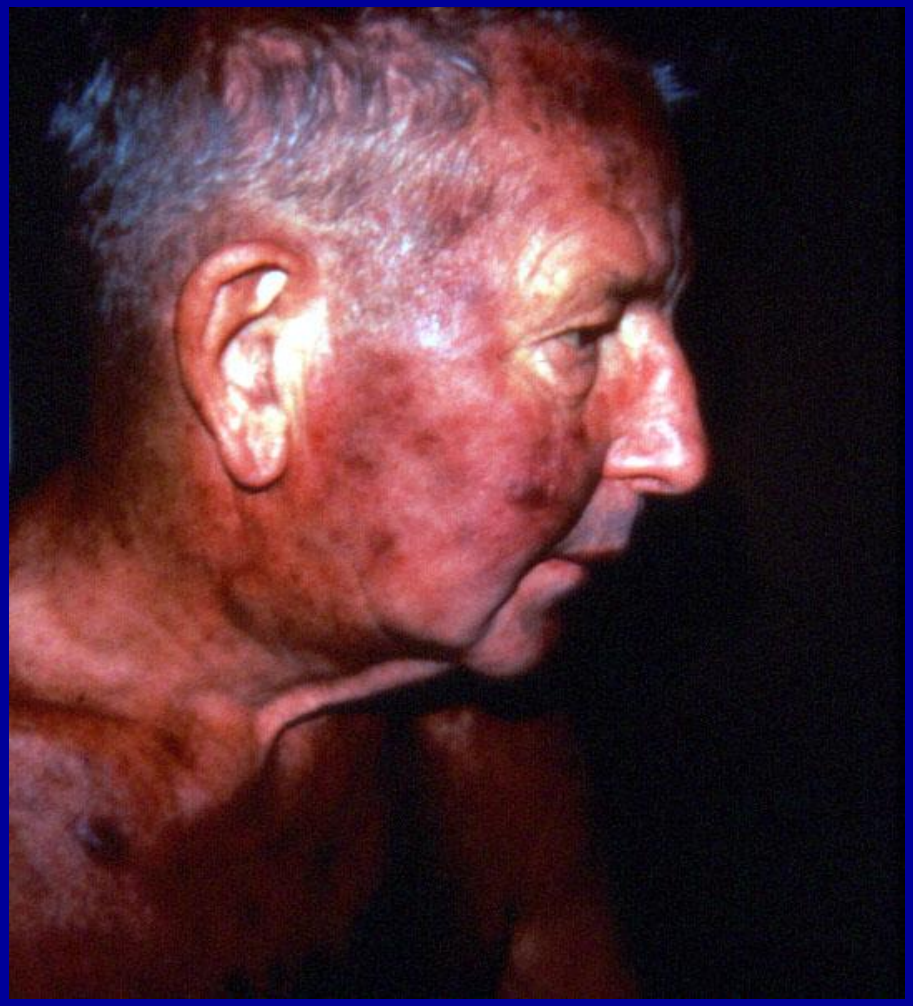
Putative Thymic Origin



Compartmentalized sclerosis

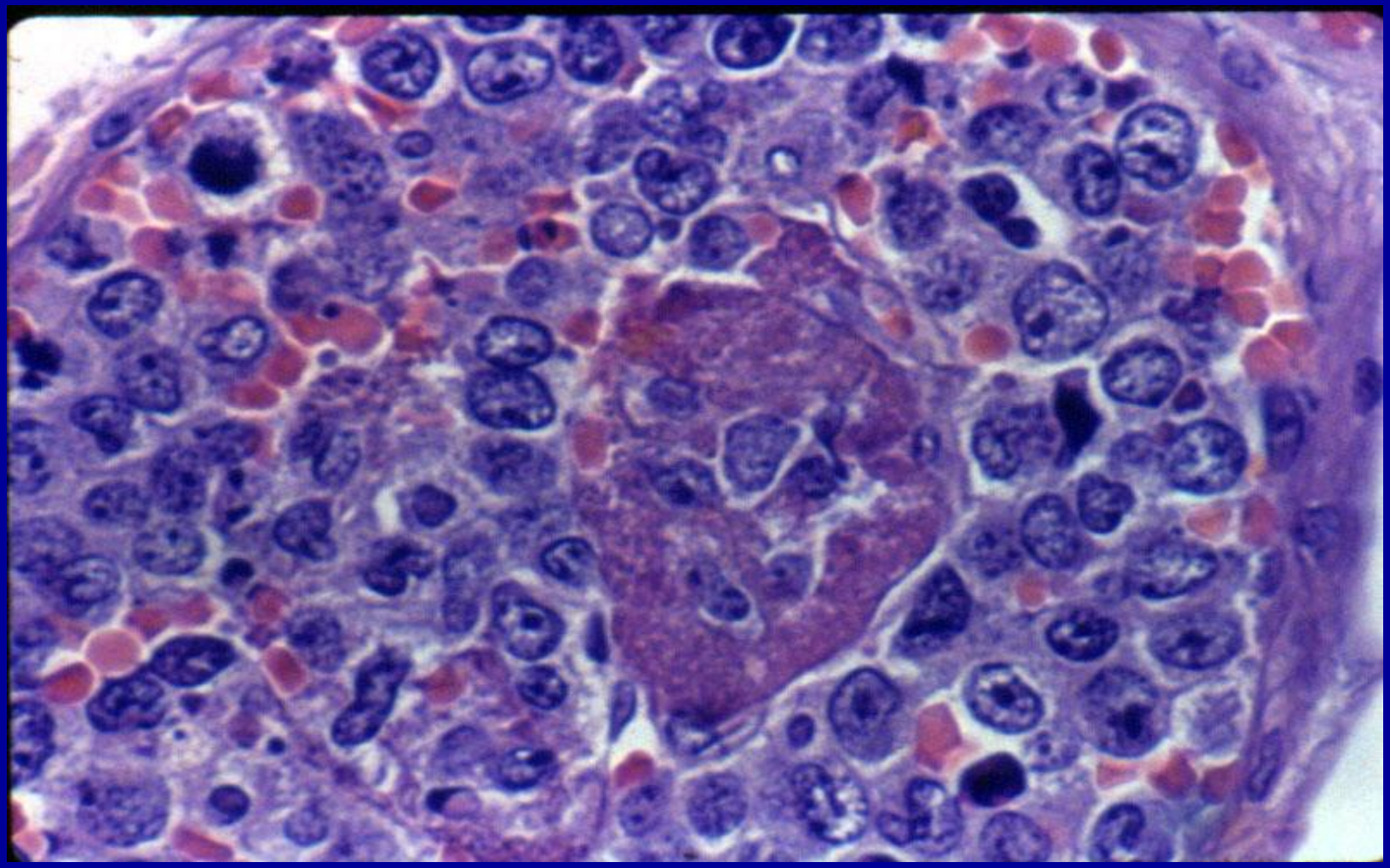


INTRAVASCULAR LYMPHOMA

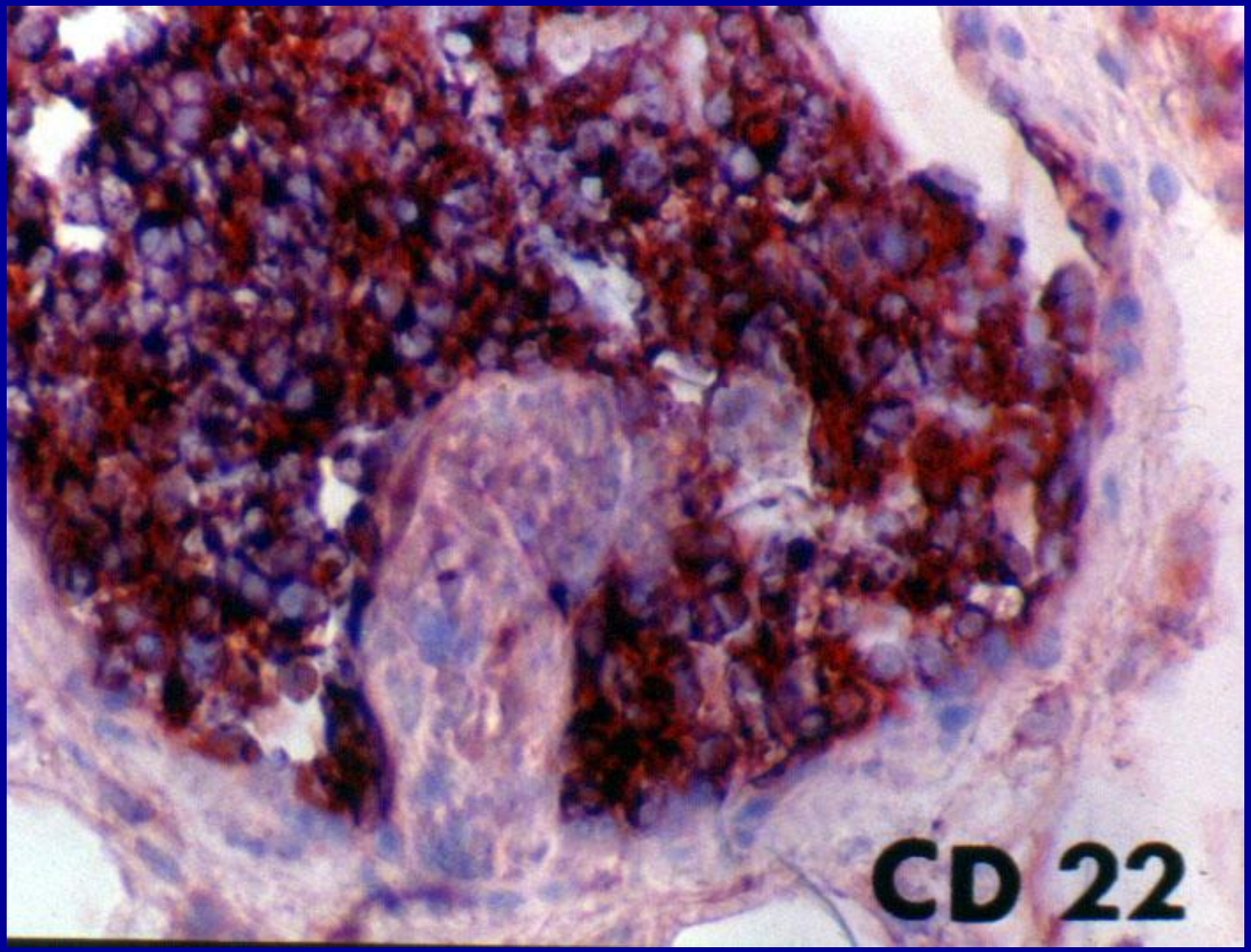


SKIN, CNS, ADRENALS
CD20+
50% 5 YEAR SURVIVAL
CHEMOTHERAPY

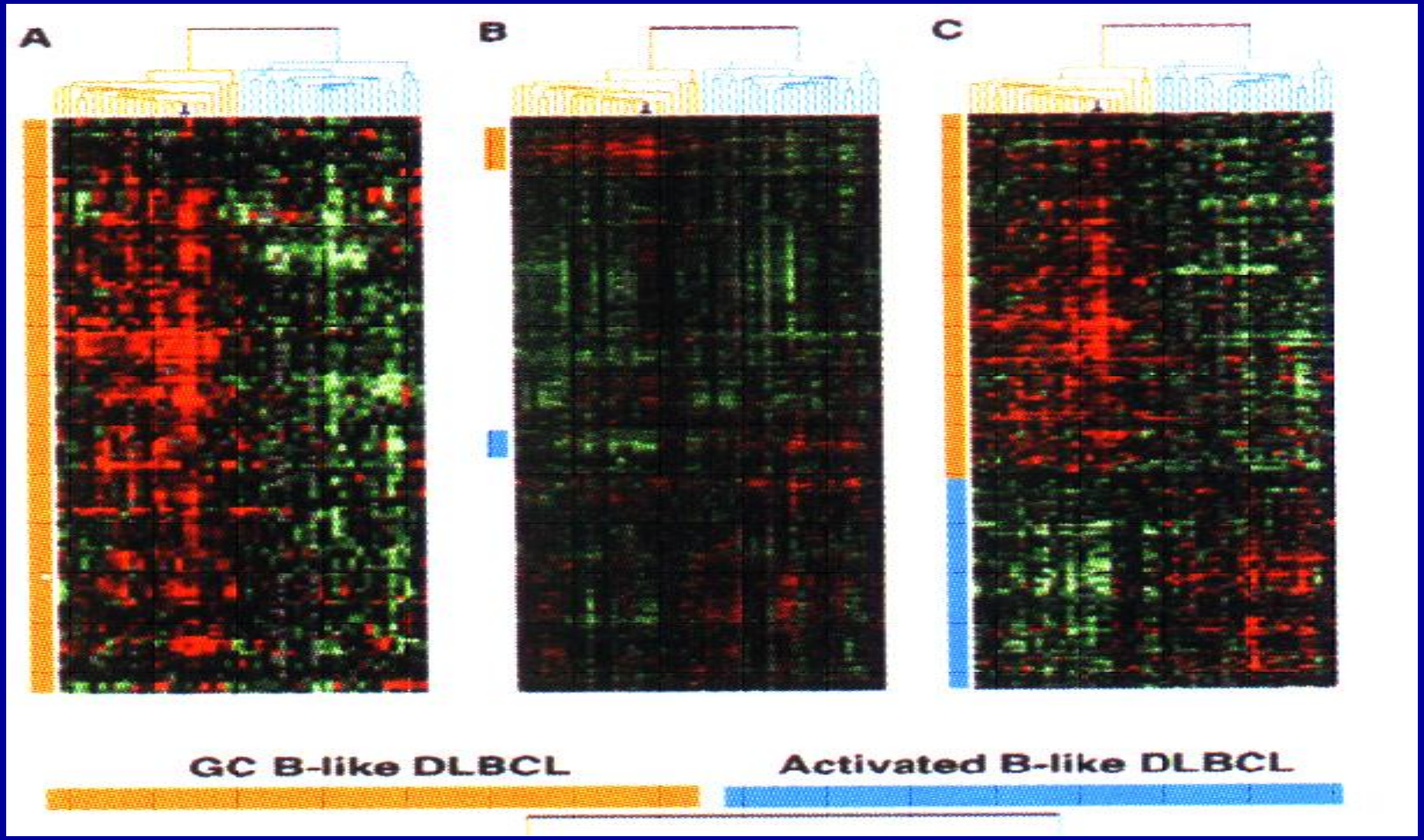
Intravascular lymphoma



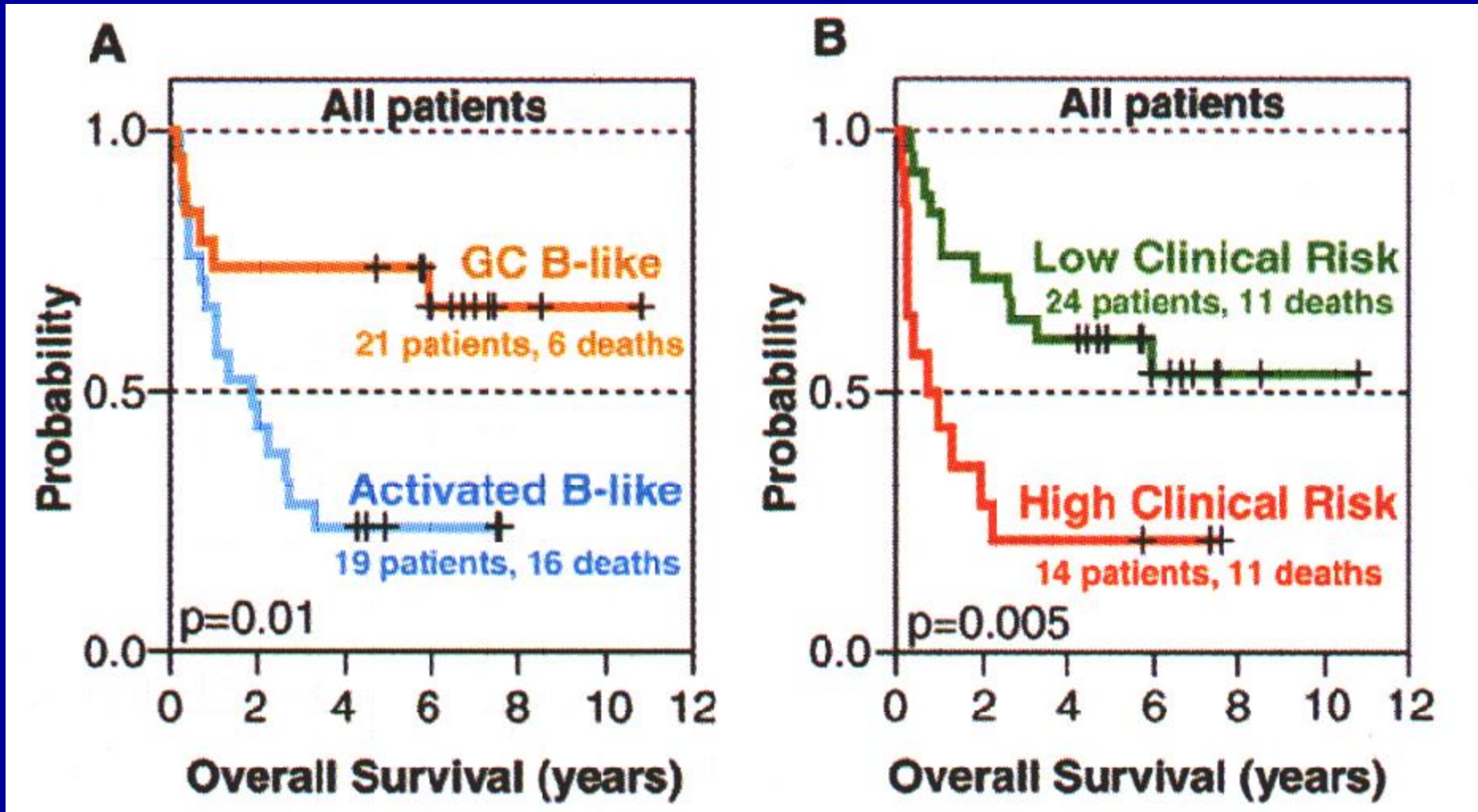
Large B cells



Gene Microarray and geneprint



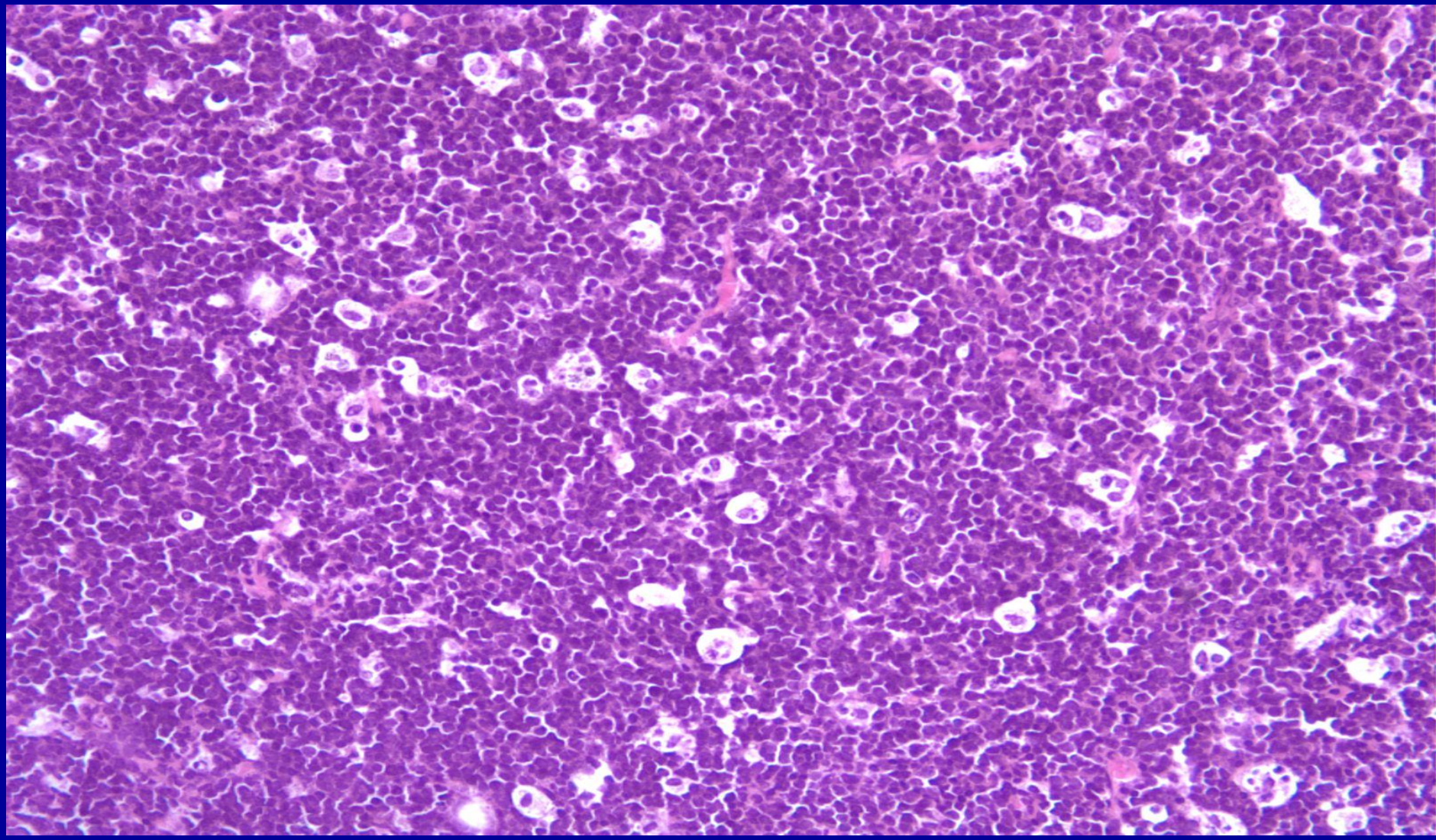
Prognostic Factor in DLBCL



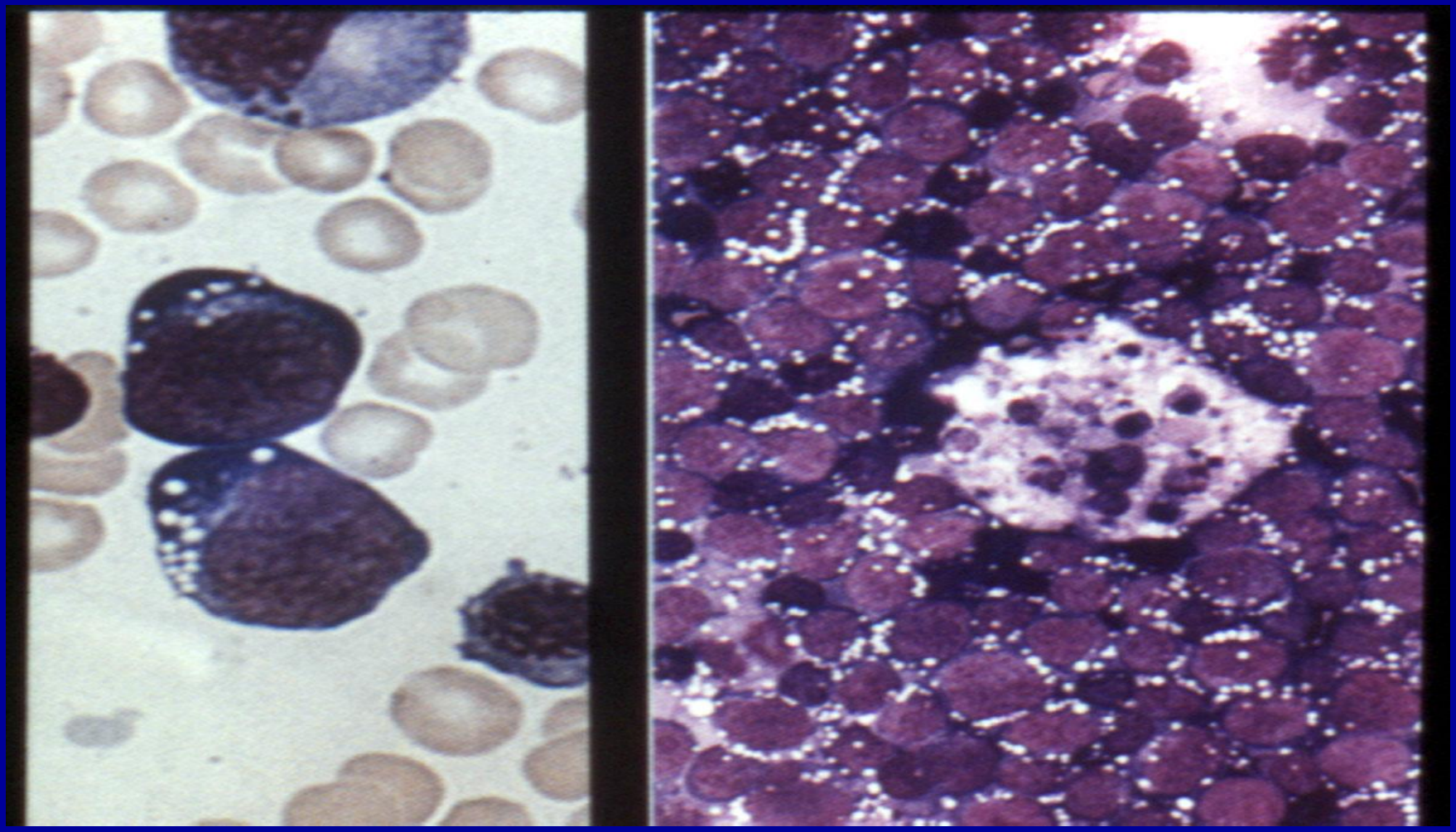
Burkitt's Lymphoma

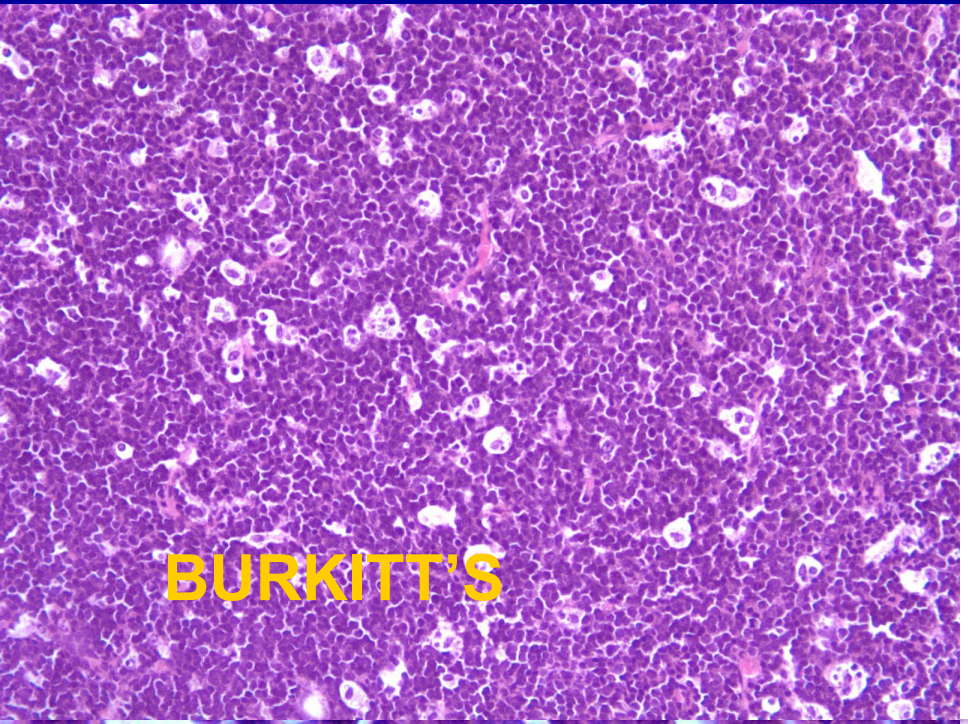
- 1/3 of all NHL in children but only 1% in adults
- Endemic-EBV+
- Sporadic-EBV-
- CD19+CD10+
- t8;14 overexpress c-myc
- small non-cleaved cells with "starry-sky" histologic pattern

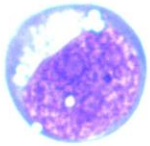
Starry sky



Cytology







BURKITT'S
CSF