Lymphomas in the Spleen

1/21/2014

Outline

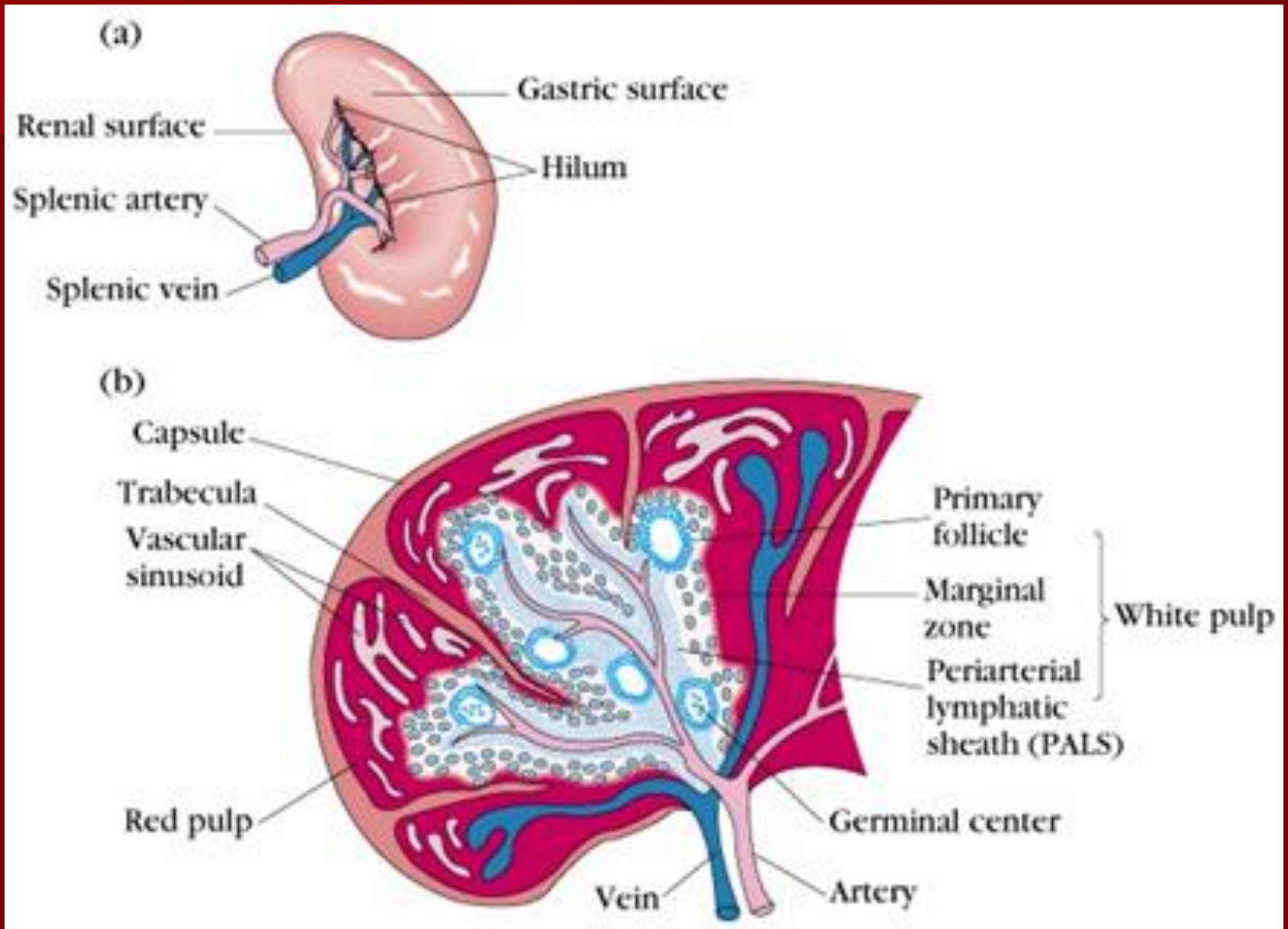
- Normal histology of the spleen
- Lymphomas in the spleen:
  -Splenic marginal zone lymphoma (0.9% of B cell lymphomas)
  -Hepatosplenic T cell lymphoma (1.4% of T cell lymphomas)
  -Splenic B cell lymphoma/leukemia, unclassifiable (provisional entity)
  -Other lymphomas (not covered here)
- Case studies

NORMAL HISTOLOGY OF THE SPLEEN

Gross Anatomy

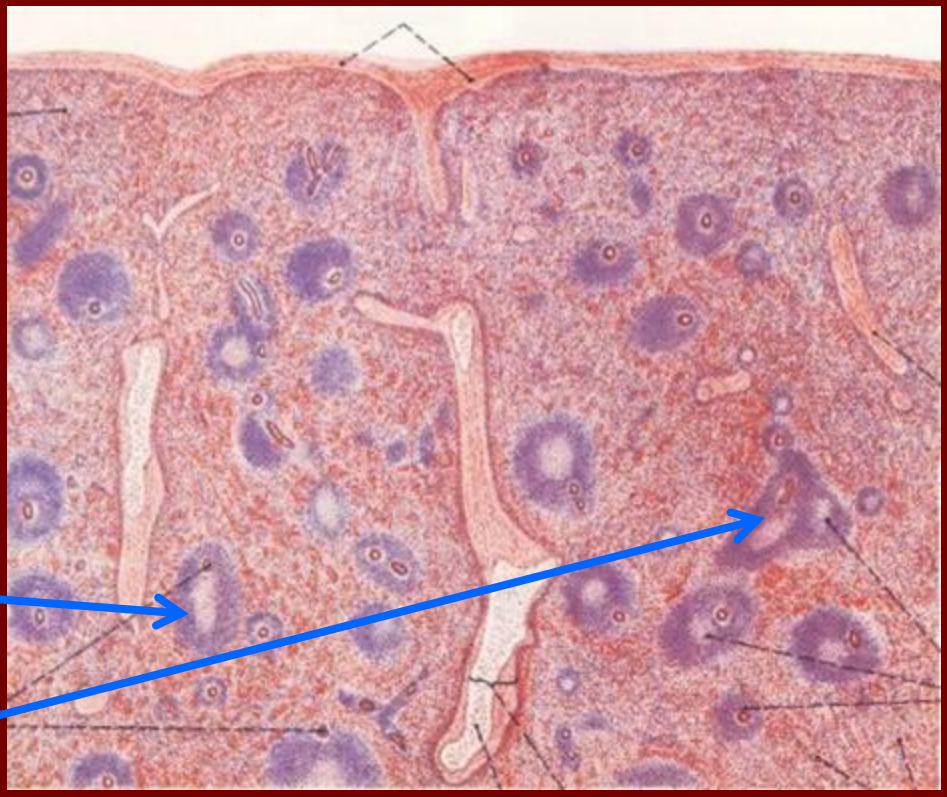
- Normal weight 150 g, SD 25 g
- Hilus, where it is penetrated by vessels and nerves which follow the extensive branching network of fibrous trabeculae.
- Accessory spleens occur in about 10 percent of individuals
- Following traumatic rupture, small nodules of splenic tissue may grow on the peritoneal surface as implants (splenosis)

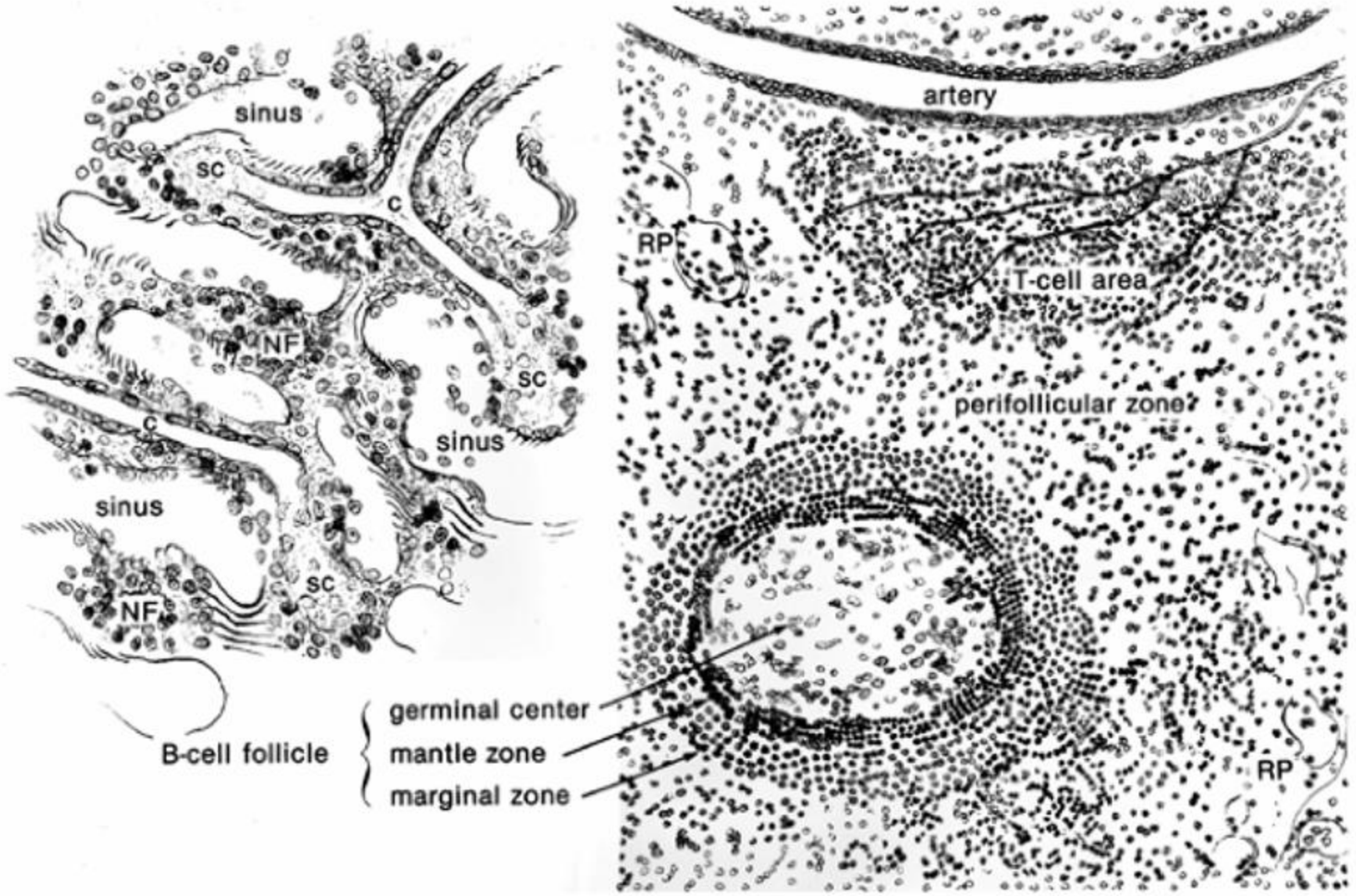
Normal spleen



White Pulp

- Comprises the lymphoid compartment of the spleen and consists of both follicular B-cell-rich areas as well as T-cell-rich periarteriolar lymphoid sheaths.

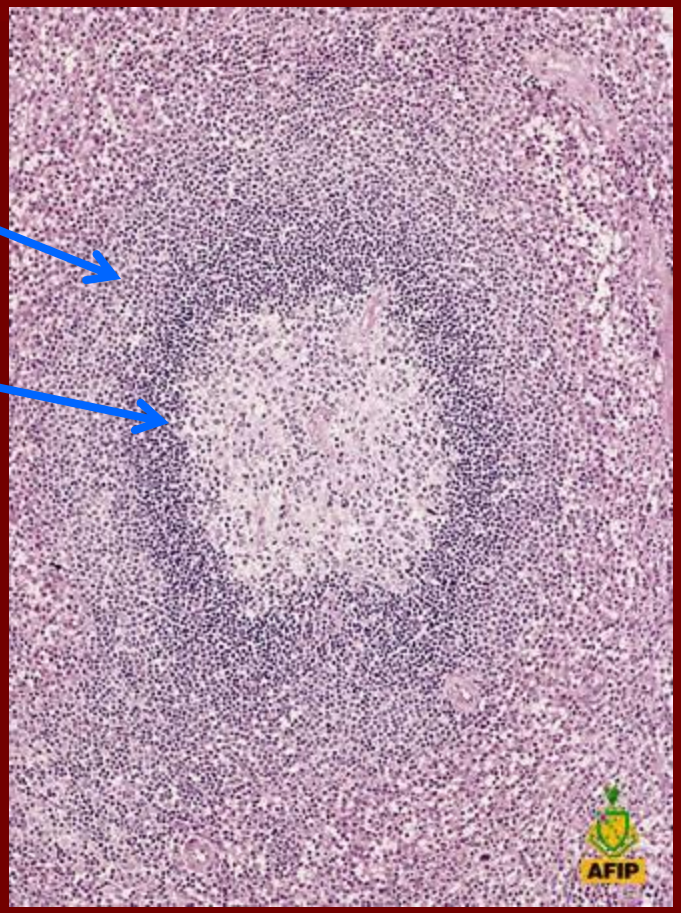



sinus
sc
c
NF
sc
sinus
c
sinus
sc
NF
B-cell follicle
germinal center
mantle zone
marginal zone
artery
RP
T-cell area
perifollicular zone
RP

Primary and Secondary B-Cell Follicles

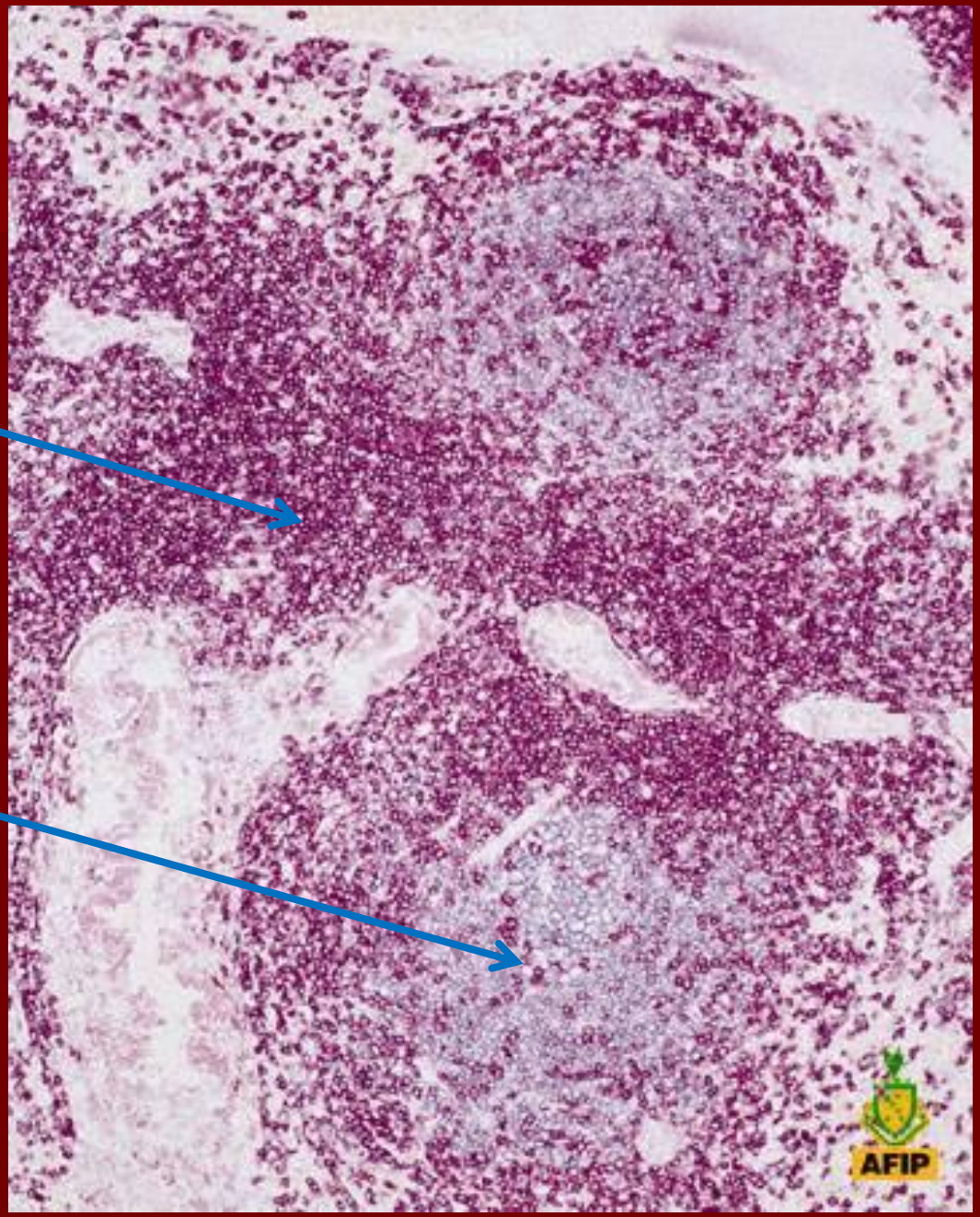
MARGINAL ZONE

- Surrounds the primary follicle and the mantle zone of secondary follicles
- Consists of a corona of medium-sized lymphoid cells with prominent pale cytoplasm



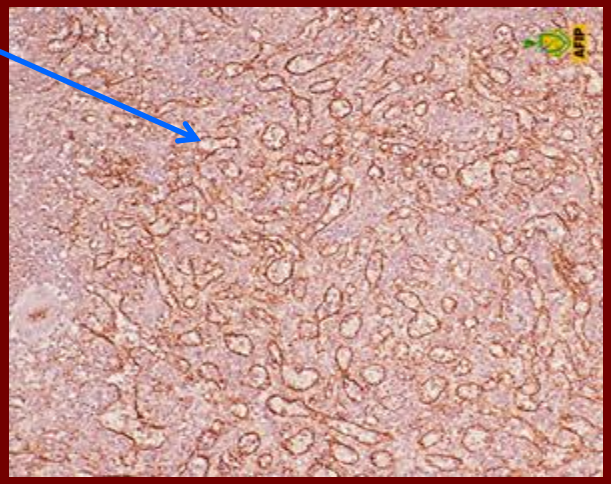
Spleen: Periarteriolar area

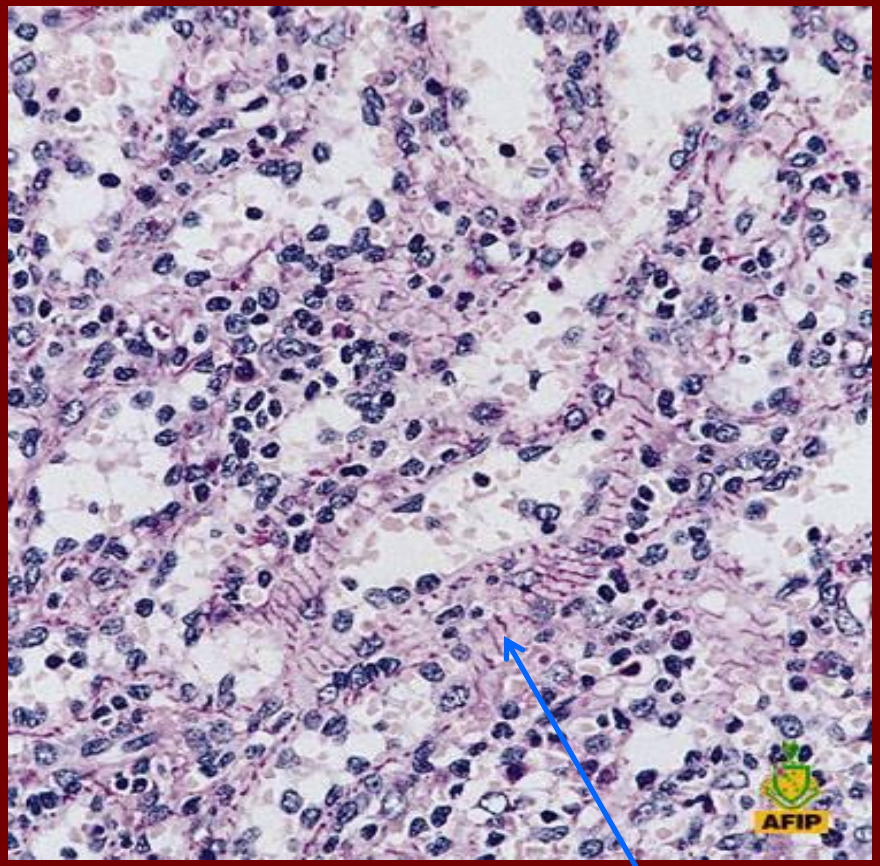
The T cells predominate in the periarteriolar lymphoid sheath (labeled red with Leu-22/ CD43). The follicles, which tend to occur at arterial branch points, are labeled blue (L26/CD20).



Sinusoids

- Are lined by tapered endothelial cells separated by slit-like spaces and surrounded by distinctive ring fibers and bridging fibers
- Stain endothelial markers (FVIII)

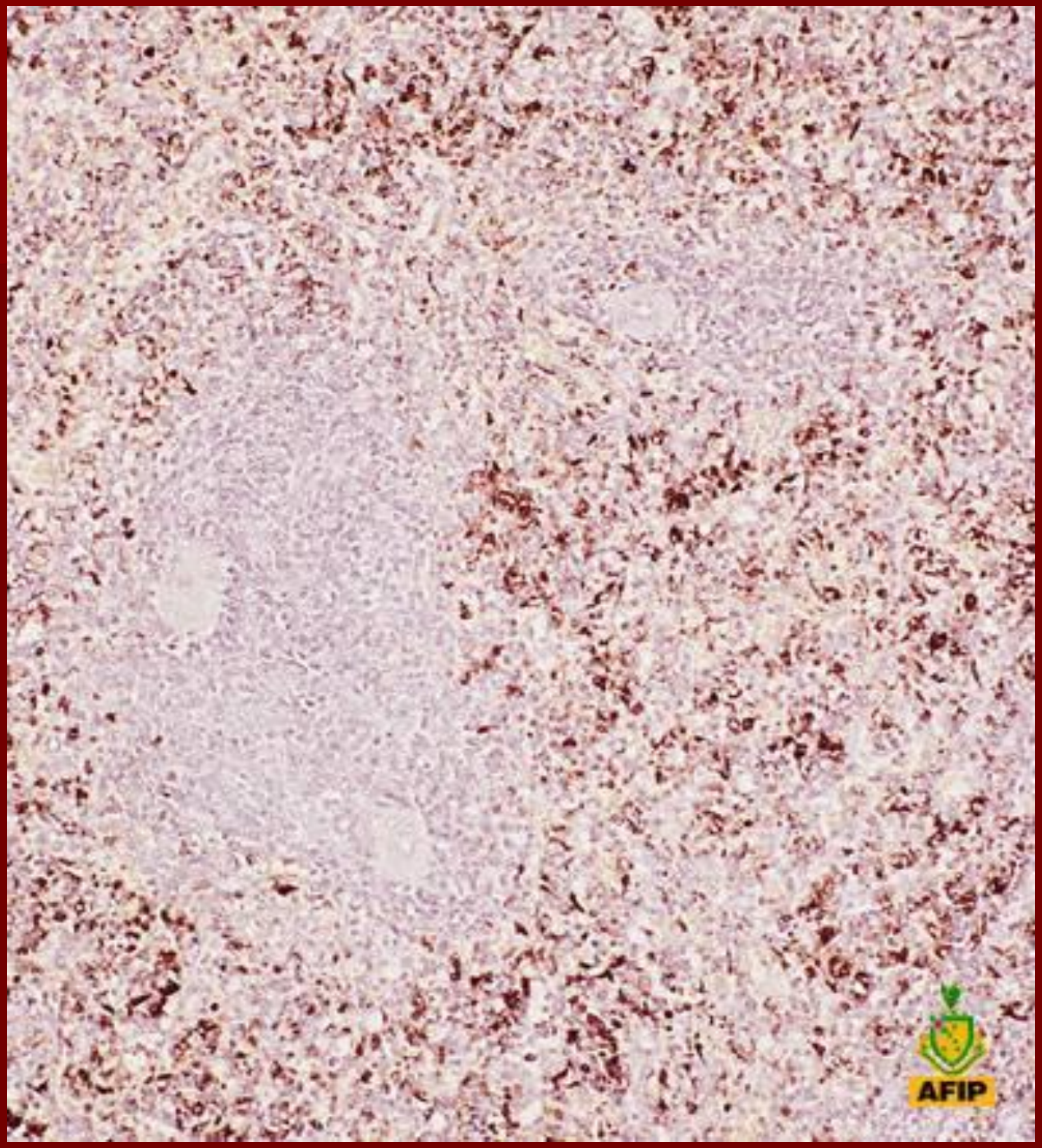




PAS stain highlights the distinctive ring fibers and bridging fibers

Splenic macrophages

Macrophages are preferentially located in the marginal zone and red pulp cords of the spleen (labeled brown with KP-1/CD68).



Splenic Marginal Zone Lymphoma

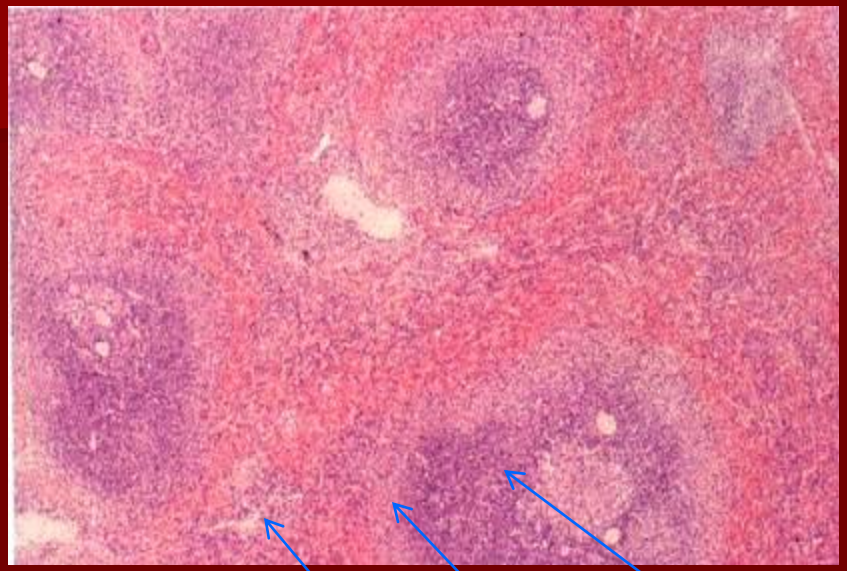
SMZL: Definition

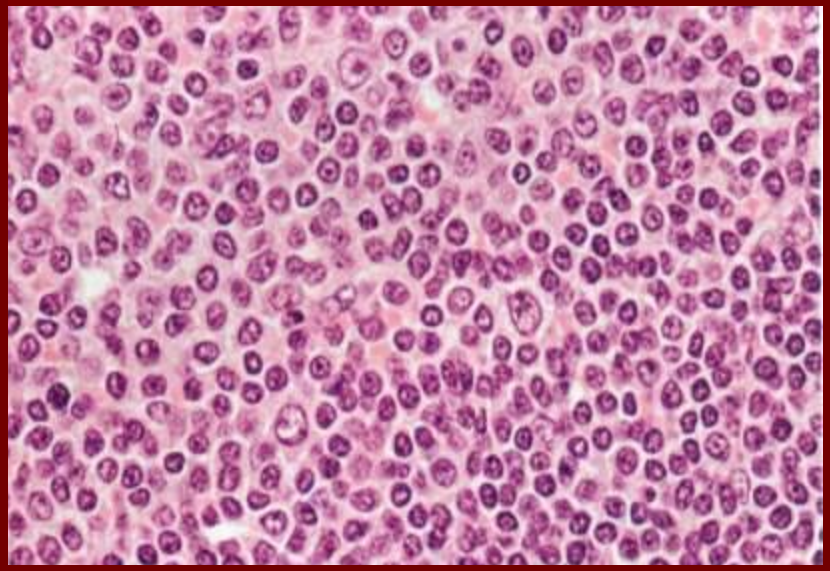
- B-cell neoplasm
- Small lymphocytes that surround and replace the splenic white pulp germinal centers, efface the follicle mantle and merge with a peripheral (marginal) zone of larger cells including scattered transformed blasts
- Both small and larger cells infiltrate the red pulp
- Hilar lymph nodes and BM are often involved
- Peripheral blood: may show villous lymphocytes
- May account for most cases of otherwise unclassifiable chronic lymphoid leukemias that are CD5(-)
- Most patients >50 y/o, F=M

SMZL

Spleen: white pulp expansion with red pulp infiltration

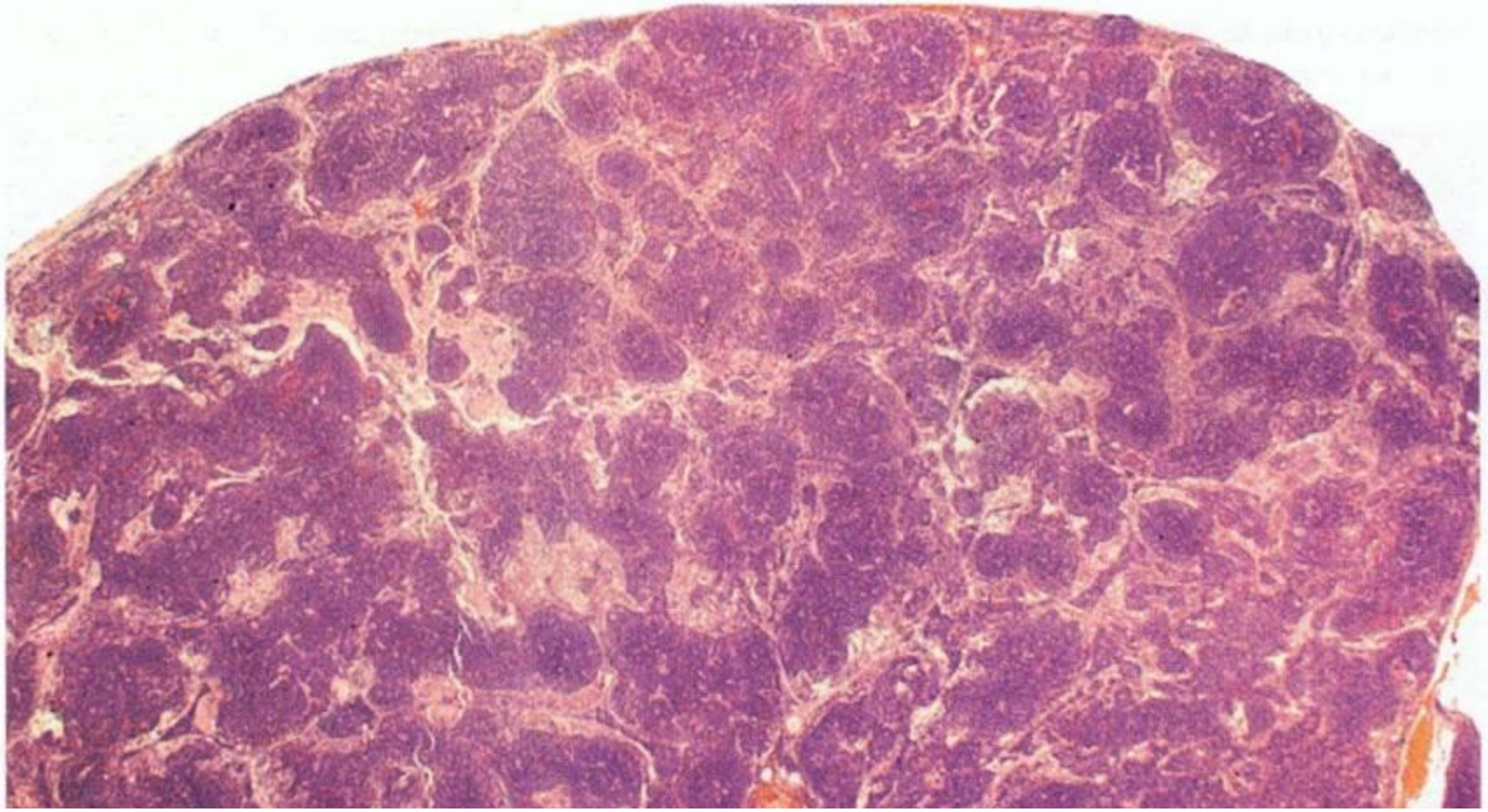
SMZL: Morphology-Spleen



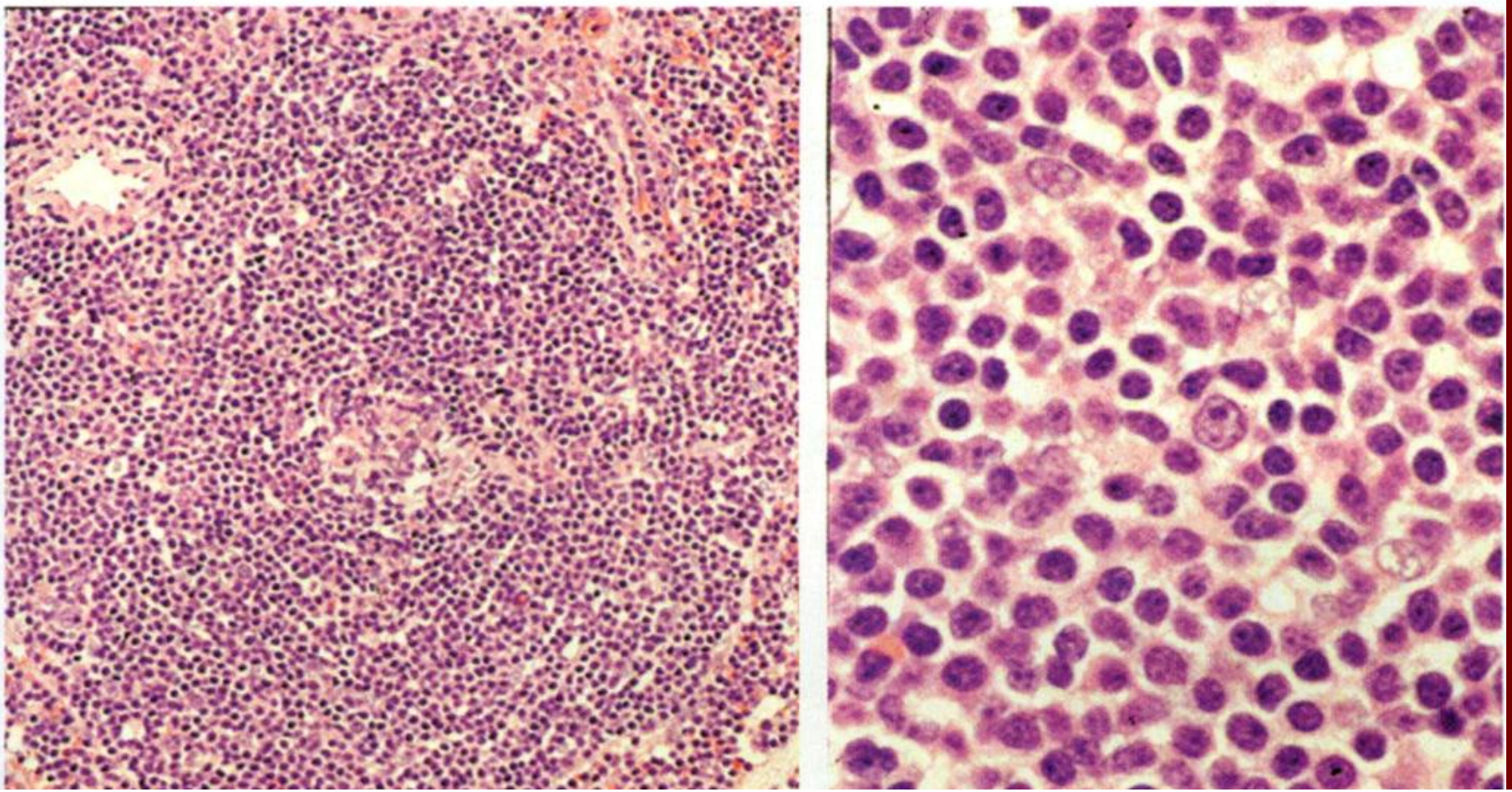


- White pulp/central zone: small round lymphocytes, surrounds, or, more commonly replaces reactive germinal centers with effacement of the normal follicle mantle.
- White pulp/peripheral zone: small to medium-sized cells with more dispersed chromatin and abundant pale cytoplasm resemble marginal zone cells and are interspersed with transformed blasts.
- Red pulp: always infiltrated, small nodules of larger cells and sheets of the small lymphocytes, which often invade sinuses

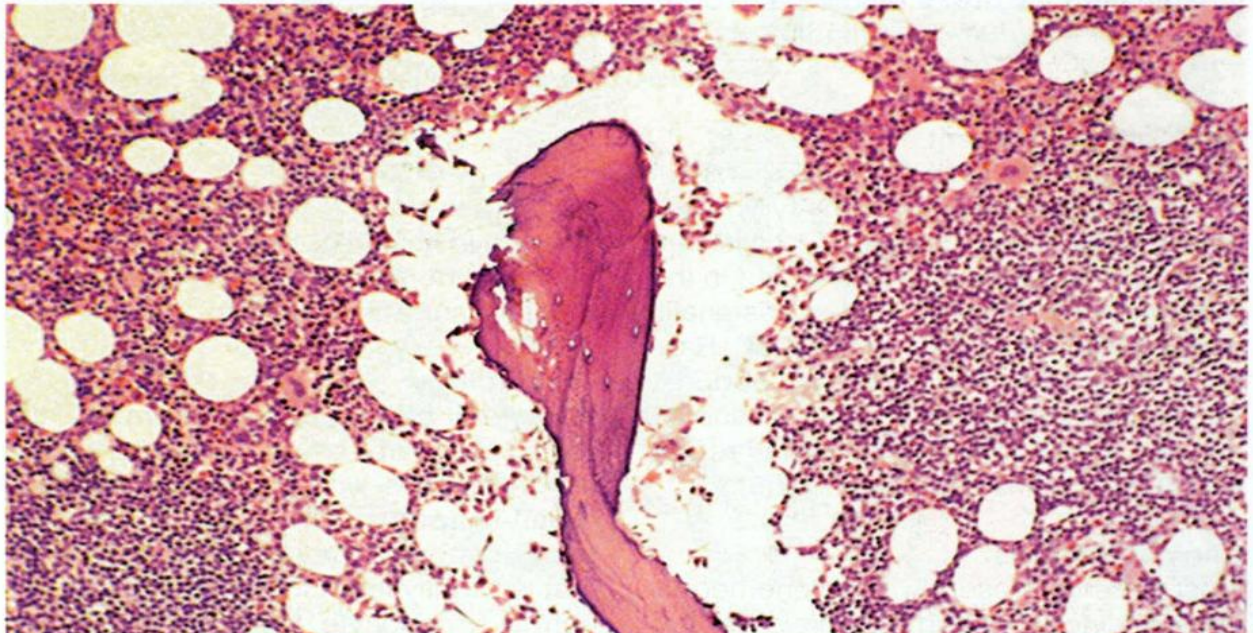
SMZL: Morphology-Hilar LN



- Sinuses are dilated
- Lymphoma surrounds and replaces germinal centers



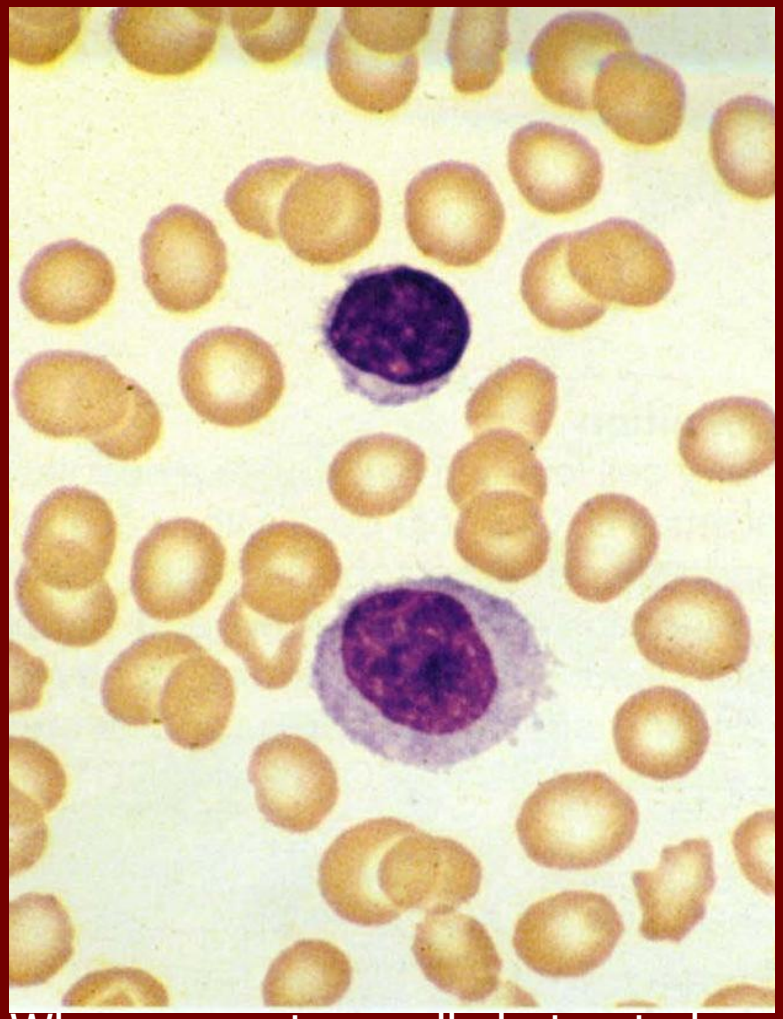
SMZL, splenic hilar lymph node



SMZL, bone marrow involvement

- Nodular interstitial infiltrate, cytologically similar to that in the lymph nodes.
- Occasionally neoplastic cells surround reactive follicles, but this is not a consistent finding

SMZL, villous lymphocytes in PB



- When present, usually but not always, have short polar villi
- Some may appear plasmacytoid

SMZL: Morphology-DDX

- Other small B-cell lymphoma/leukemias: CLL, HCL, MCL, FL, LPL
- Nodular pattern on BM excludes HCL, but BM morphology may not be sufficient to distinguish from others
- PB villous lymphocytes are helpful
- Flow cytometry of PB or BM very helpful

SMZL: Immunophenotype

- Positive: sIgM, sIgD, CD20, CD79a
- Negative: CD5, CD10, CD23, CD43, cyclin D1, CD103

SMZL: Genetics-Antigen Receptor Genes

- IgH and Ig light chain genes are rearranged
- Most cases have somatic mutation
- Intraclonal variation: ongoing mutations

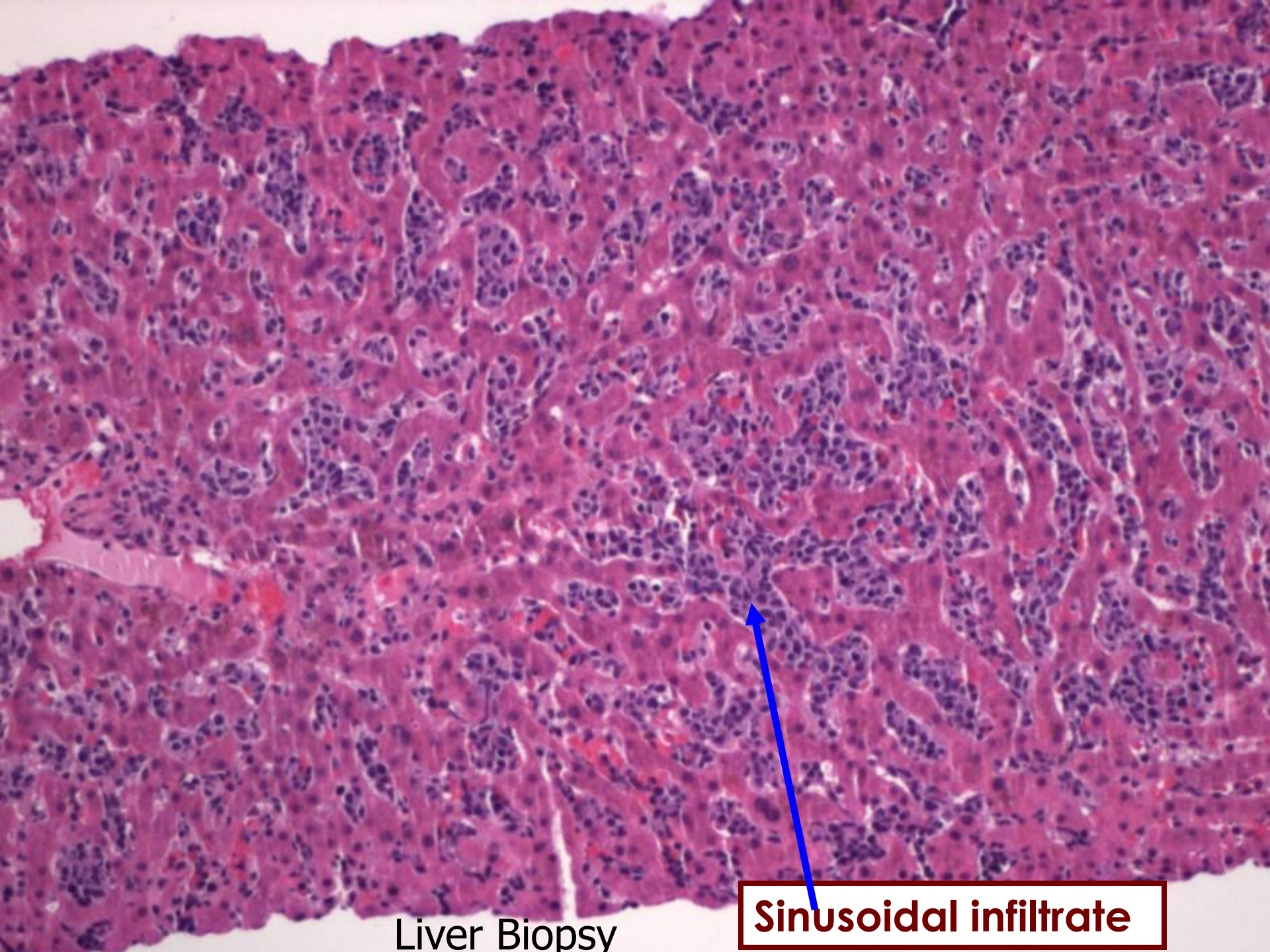
SMZL: Genetics-Cytogenetics

- Allelic loss of 7q21-32: 40% of cases. Dysregulation of *CDK6* was reported.
- No *BCL2* rearrangement. No t(14;18).
- No *BCL1* rearrangement. No t(11;14).
- Trisomy 3 and t(11;18), common in MALT, are uncommon in SMZL. Trisomy 3 reported in 17 cases; no t(11;18) confirmed cases

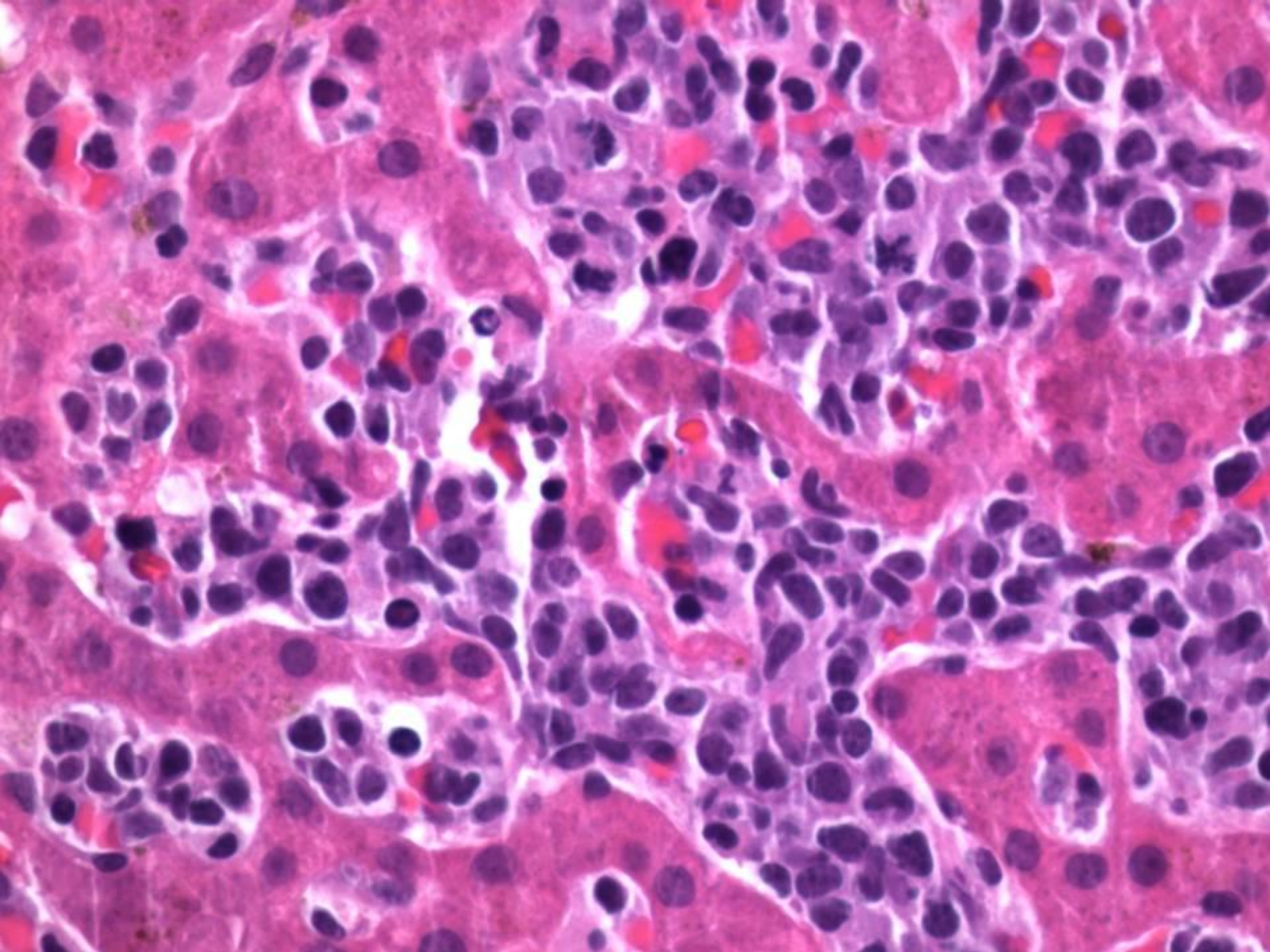
Hepatosplenic T-cell Lymphoma

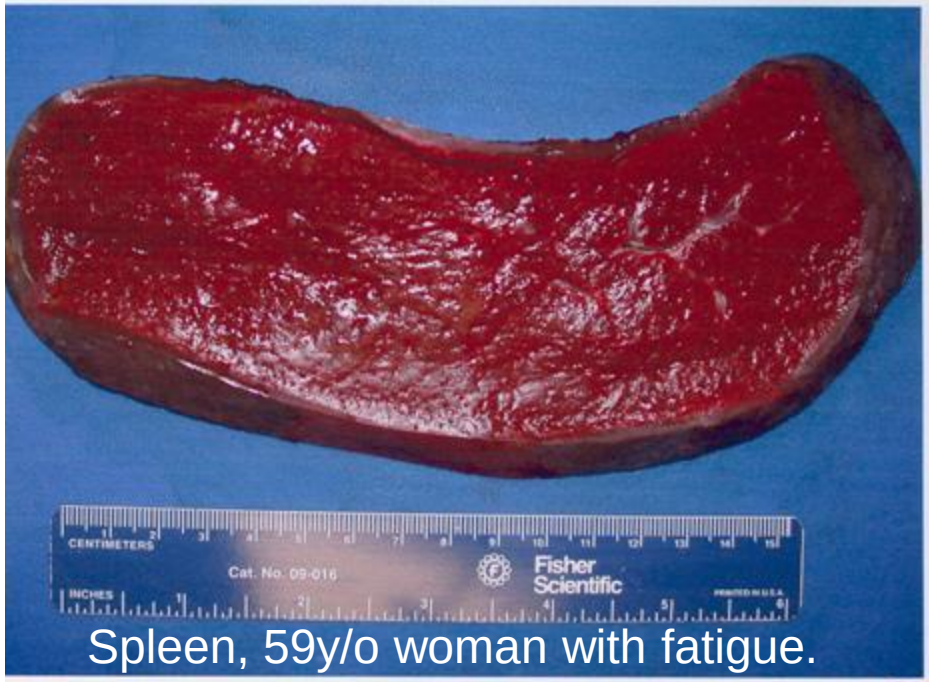
Hepatosplenic T-cell Lymphoma

- Extranodal and systemic lymphoma usually of cytotoxic T-cells of the γδ type
- Marked sinusoidal infiltration seen in the spleen, liver and bone marrow
- Patients present with marked hepatosplenomegaly but no lymphadenopathy
- Bone marrow almost always involved
- More common in immunosuppressed patients

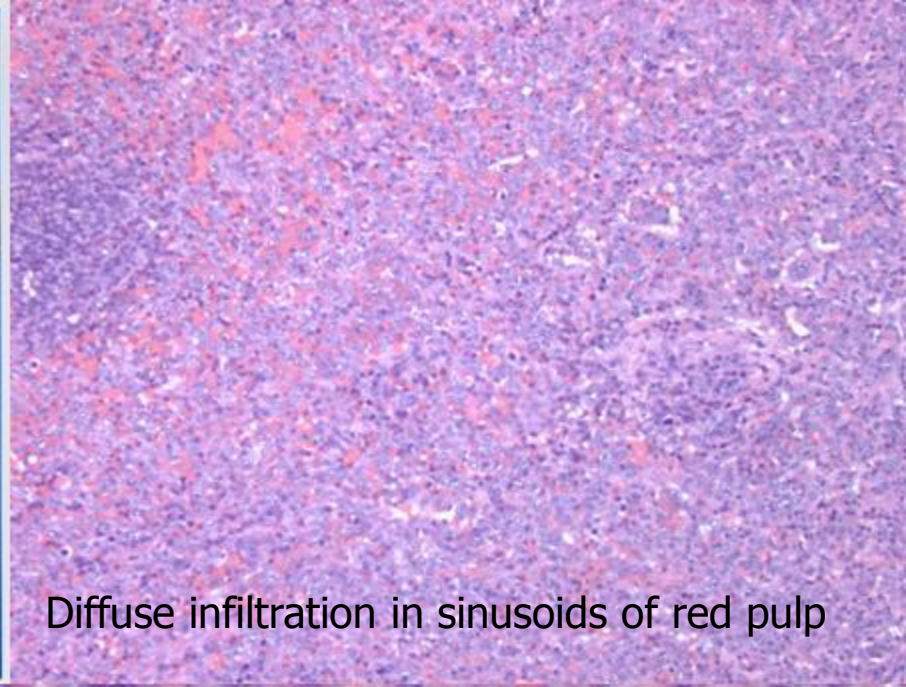


Liver Biopsy

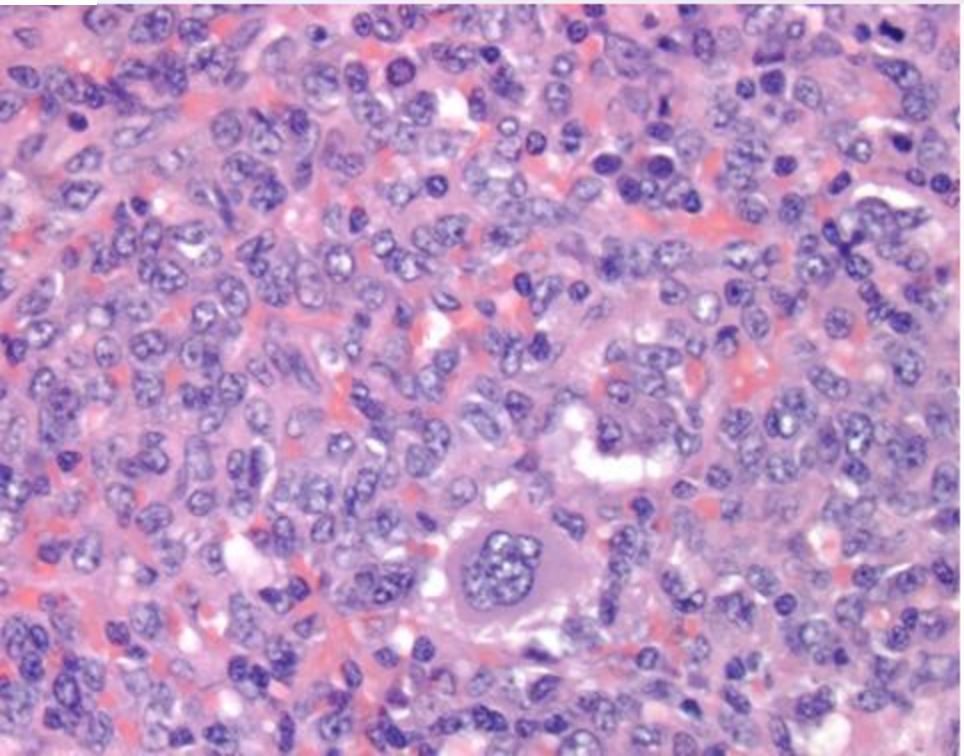


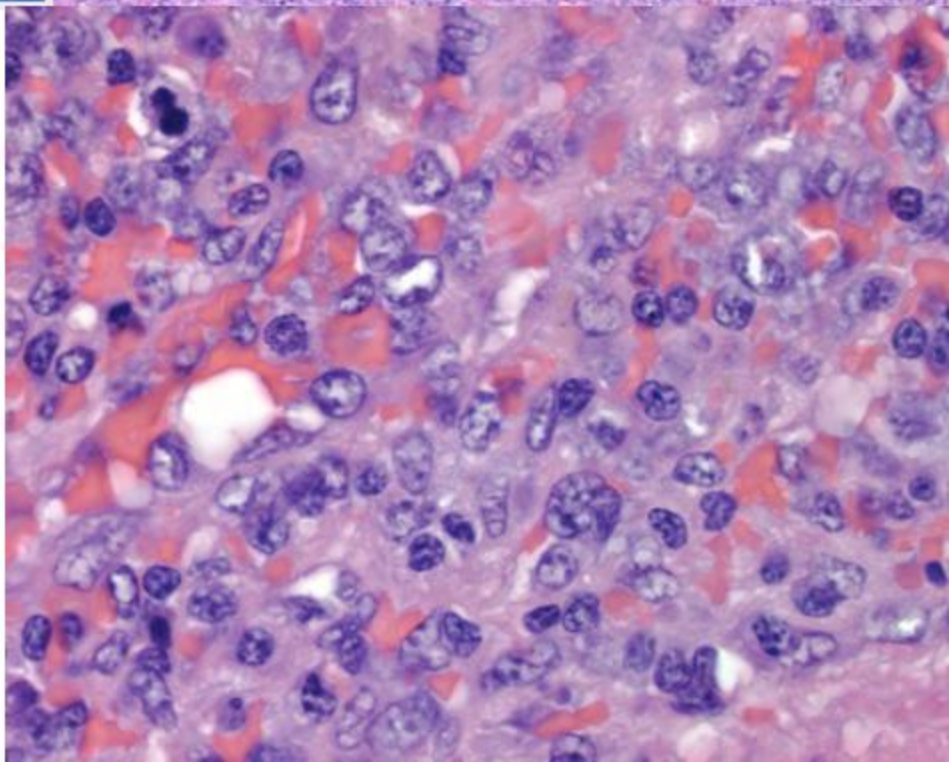


Spleen, 59y/o woman with fatigue.



Diffuse infiltration in sinusoids of red pulp

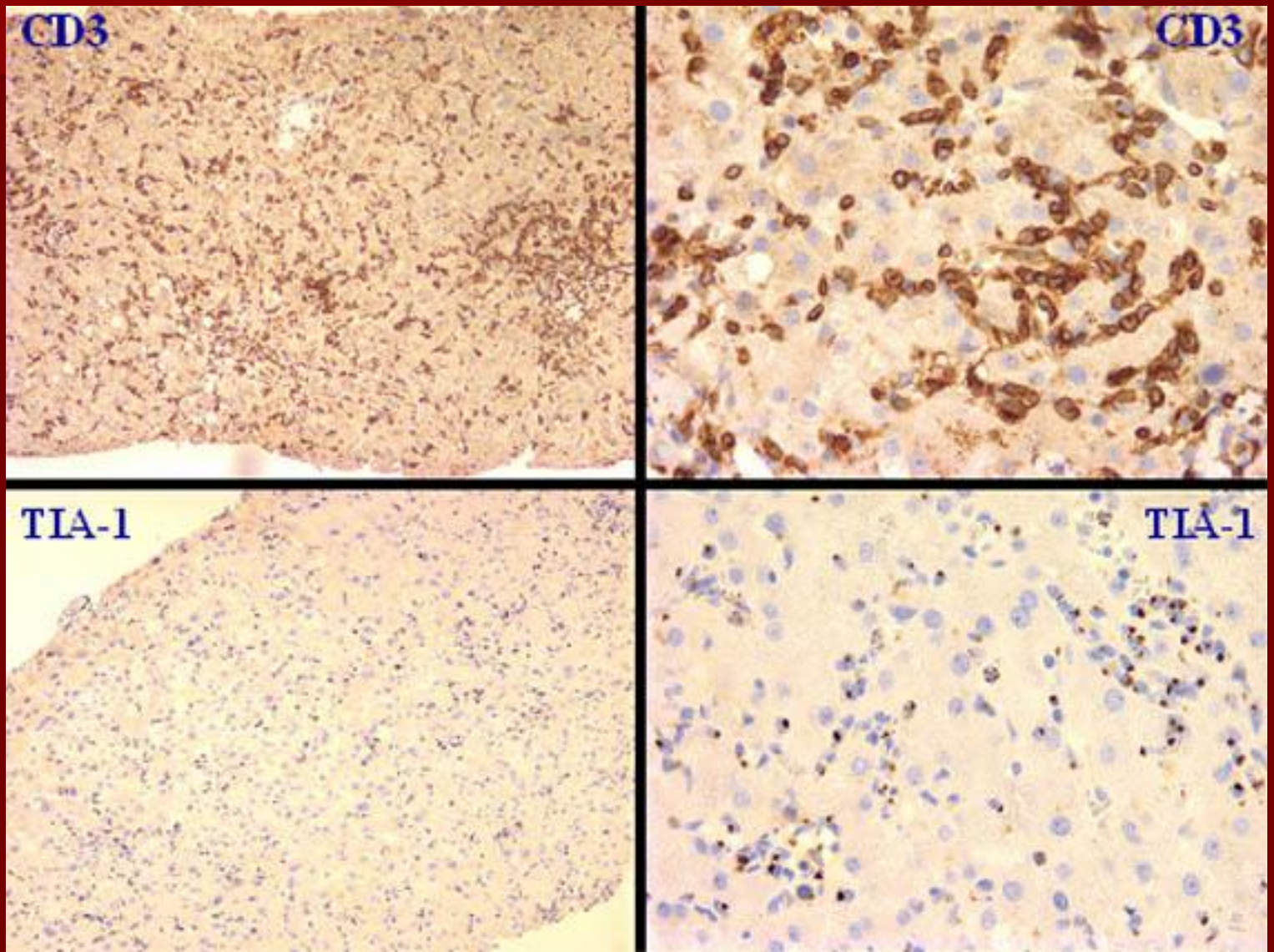




Hepatosplenic T-cell Lymphoma

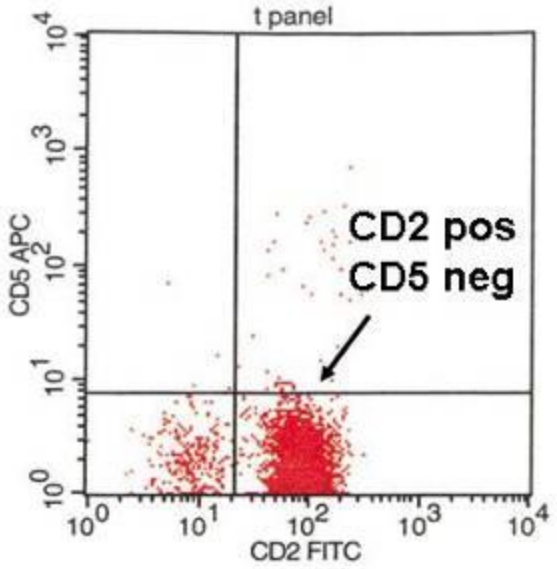
- Immunophenotype
  - CD3+, CD4-, CD8-, CD5-
  - TCRδ1+, TCRαβ-
  - Positive for cytotoxic protein TIA-1
- Genetics
  - TCR γ gene rearrangement
  - Isochromsome 7q in all cases studied
  - Sometimes other abnormalities such as trisomy 8

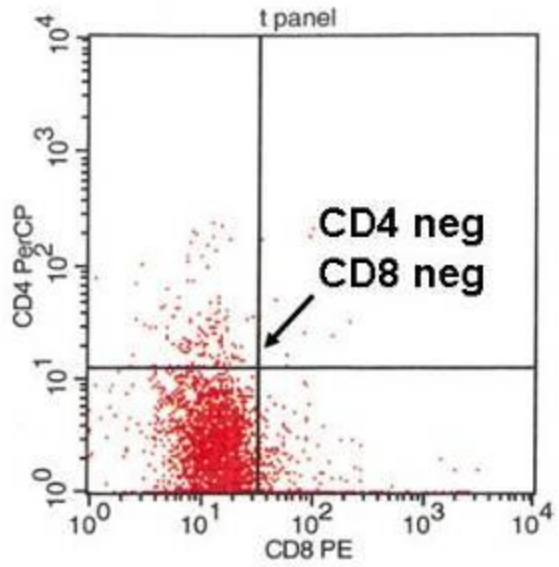
Hepatosplenic T-cell Lymphoma

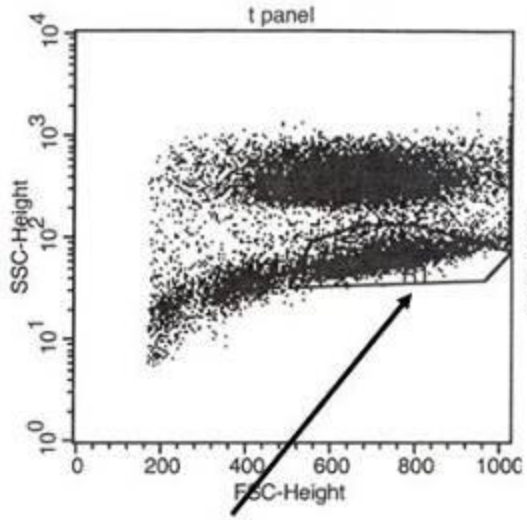


Hepatosplenic T-cell Lymphoma
Bone marrow Flow Cytometry

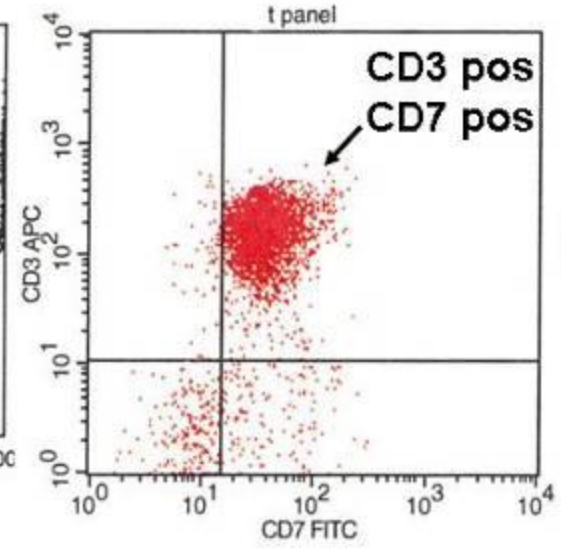
Blast-like cell

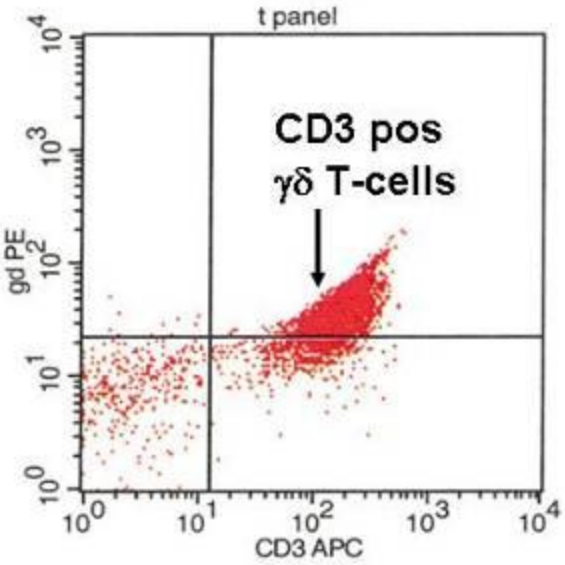




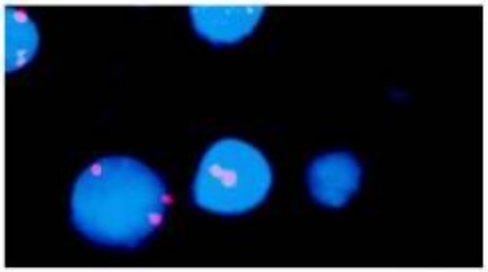


Large Cells
By Light Scatter

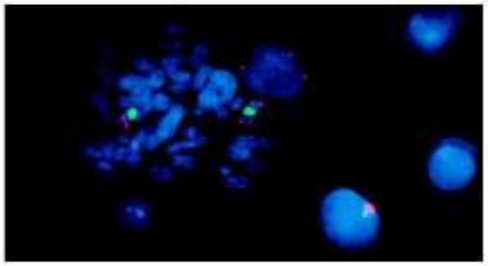




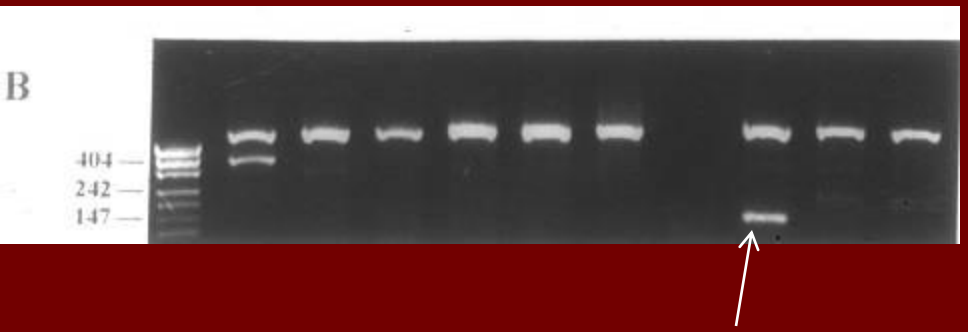
Hepatosplenic T-cell Lymphoma



Trisomy 8: Red chromosome 8 centromere



Isochromosome 7:
Green: chromosome 7 Centromere
Red: 7q3.1



Clonal V-delta-1-J-delta-1 rearrangement (Panel B, lane 1)

Prognosis

- Variable
- Some pts respond well to therapy and others die of disseminated disease despite aggressive therapy

Splenic B cell lymphoma/leukemia, unclassifiable

Splenic B cell lymphoma/leukemia, unclassifiable

- Small B-cell clonal lymphoproliferations involving the spleen, but which do not fall into any of the other types of B-cell lymphoid neoplasms recognized in the WHO classification.
- Two subtypes:
  - Splenic diffuse red pulp small B-cell lymphoma
  - Hairy cell leukaemia-variant (HCL-v)

Splenic diffuse red pulp small B-cell lymphoma

- Diffuse pattern of involvement of the red pulp, characteristic intrasinusoidal aggregates
- In contrast to SMZL, the tumour shows an absence of follicular replacement, biphasic cytology or marginal zone infiltration. The neoplastic infiltrate is composed of a monomorphous population of small to medium-sized lymphocytes, with round and regular nuclei

Hairy cell leukaemia-variant (HCL-v)

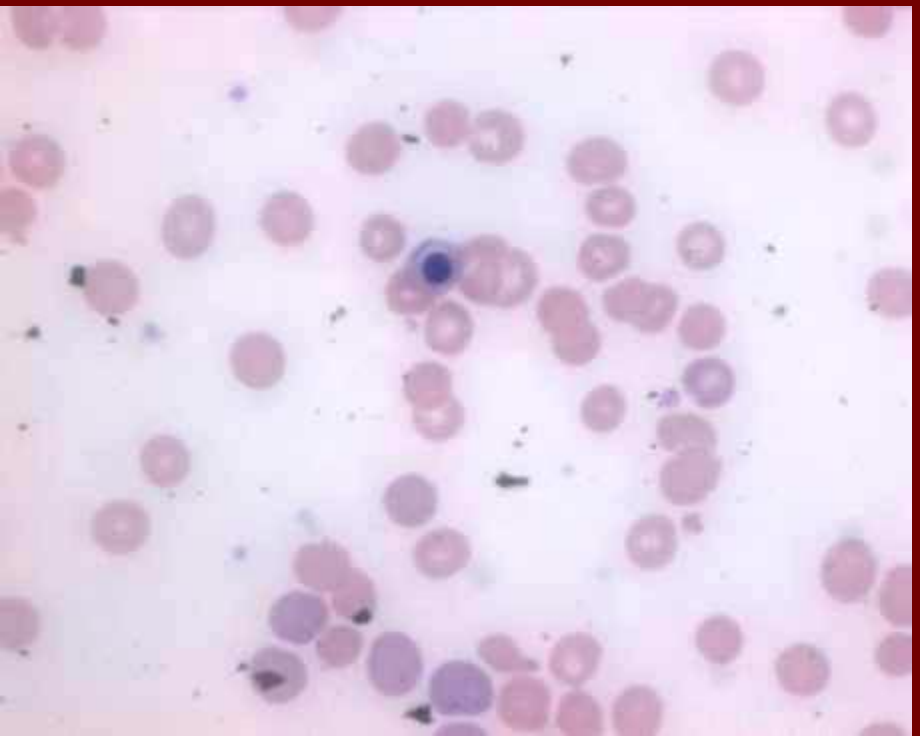
- Cases of B chronic lymphoproliferative disorders that resemble classic HCL but exhibit variant features (i.e. leukocytosis, presence of monocytes, cells with prominent nucleoli, cells with blastic or convoluted nuclei, and/or absence of circumferential shaggy (hairy contours)
- Variant immunophenotype (i.e. absence of CD25, annexin-1, or TRAP)

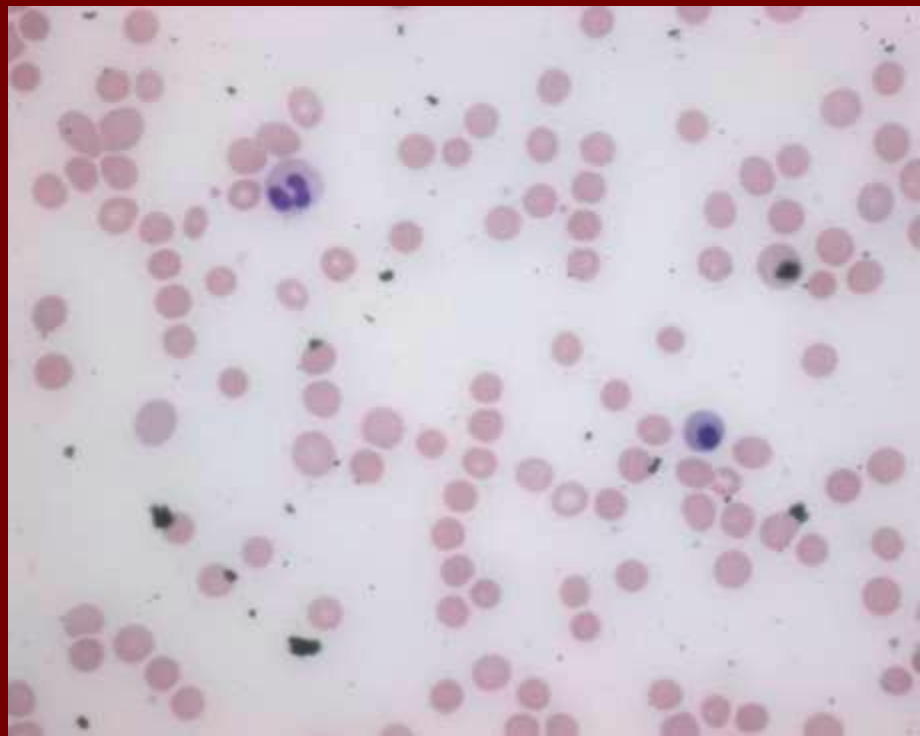
Case 1: patient CG

30 y/o male, PMHx of liver disease of unknown etiology and hemolytic anemia

Peripheral smear

- - Macrocytic anemia, severe
  - Leukopenia, mild
  - Thrombocytopenia, mild

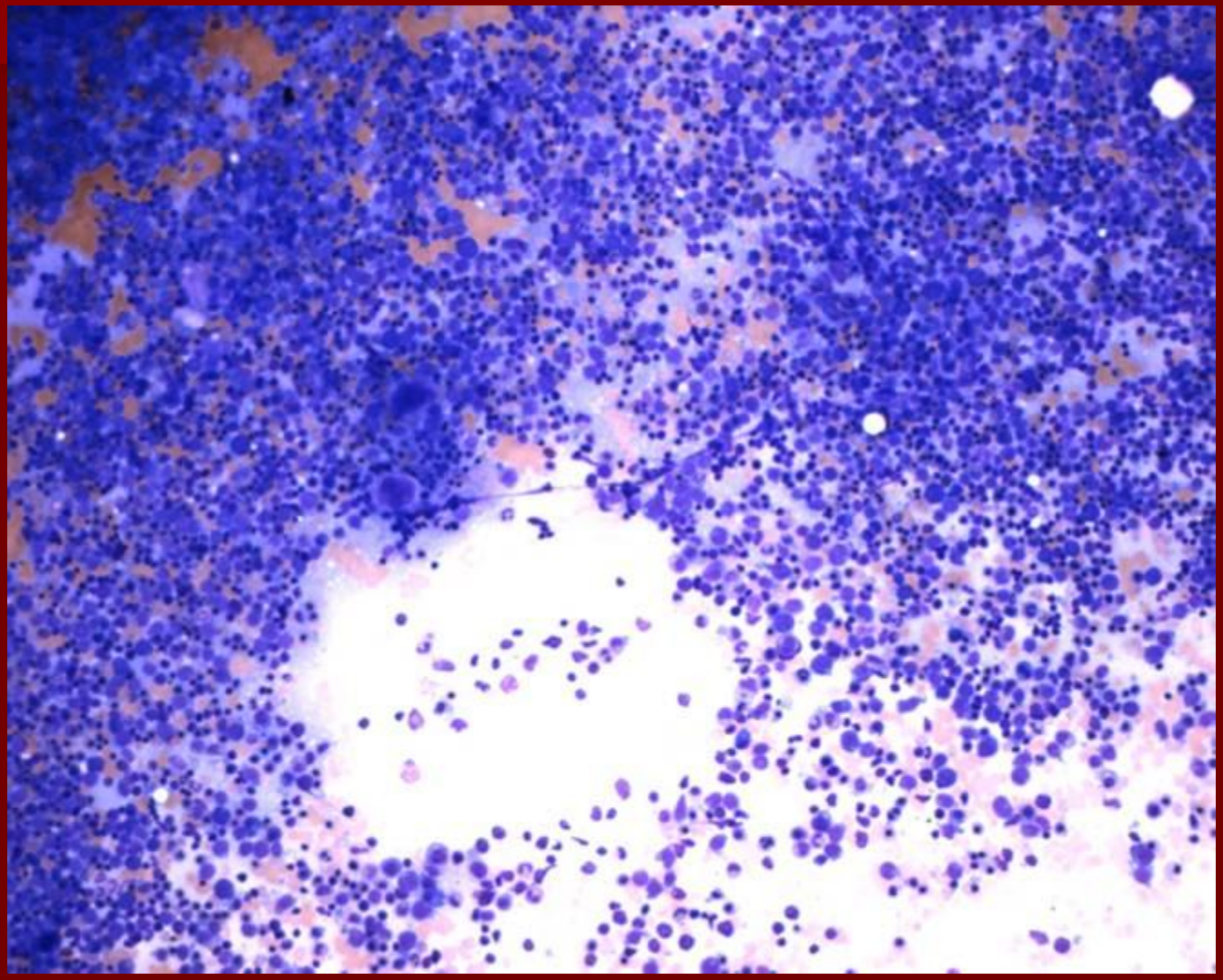


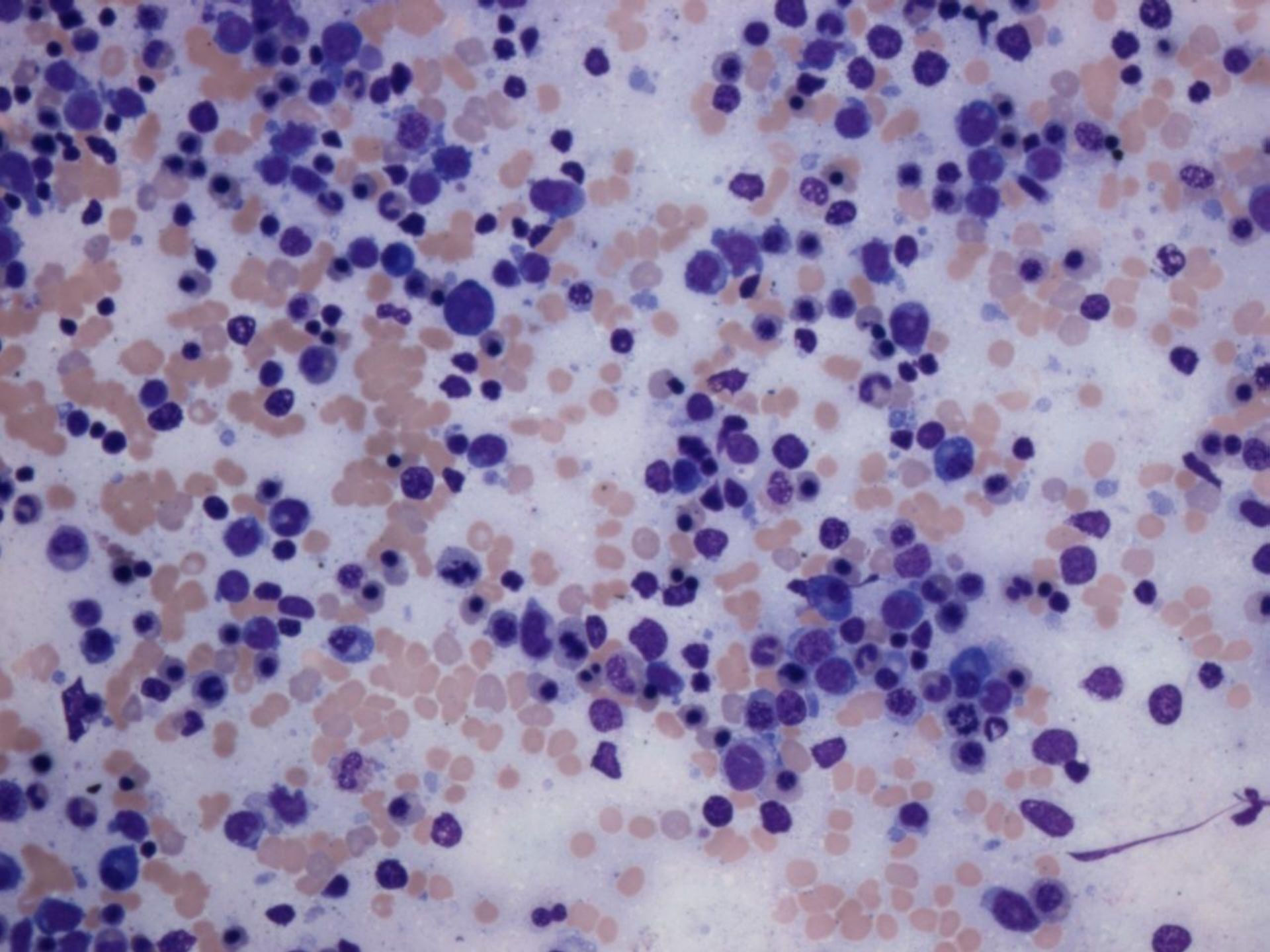


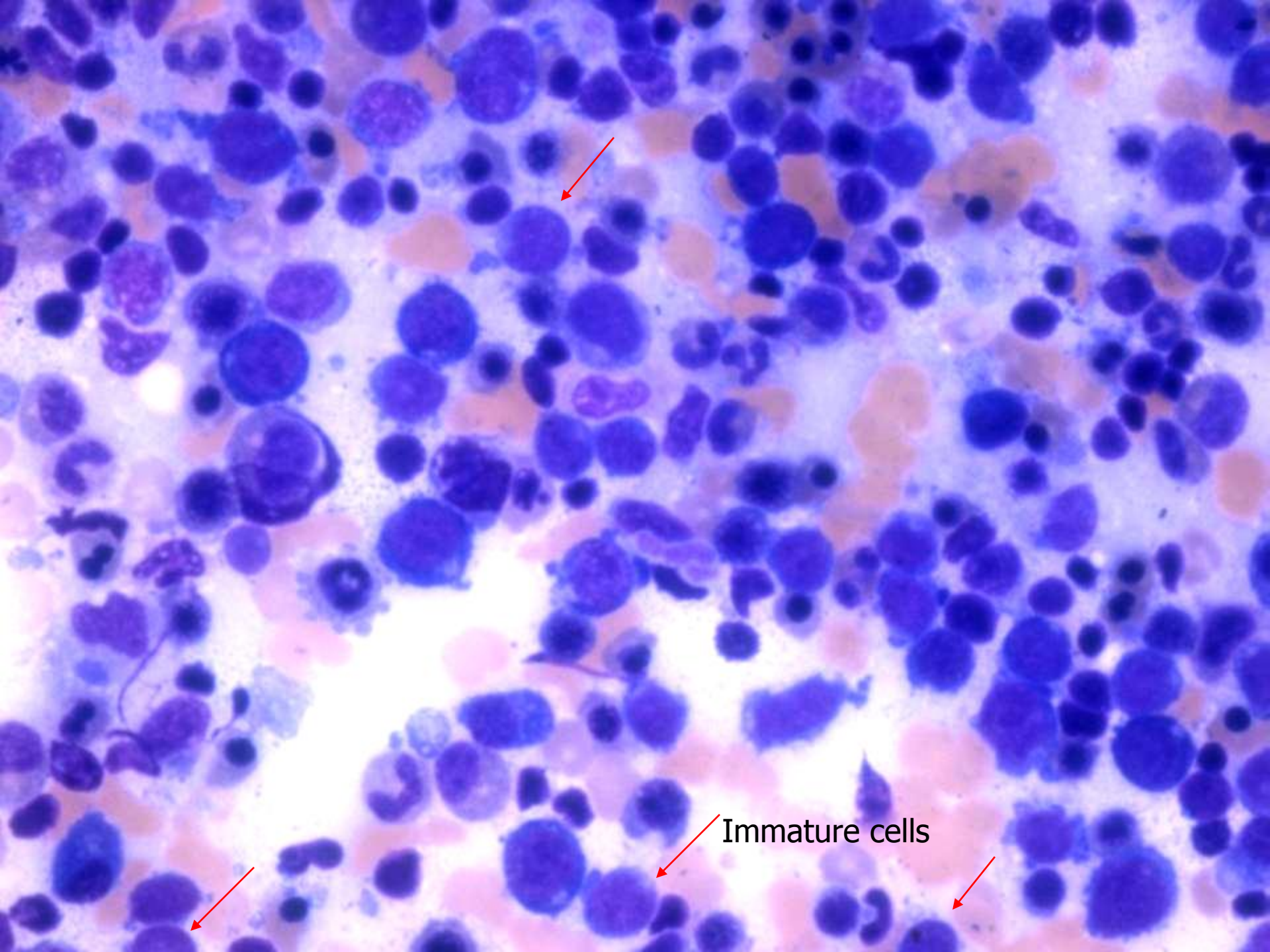
PERIPHERAL HEMOGRAM

RBC	1.42 M/uL
HGB	5.8 g/dL
HCT	16.6 %
MCV	117 fL
MCH	40.5 pg
MCHC	34.7 g/dL
RDW	17.2 %
RETIC%	12.2 %
PLT	136 K/uL
WBC	4.4 K/uL
BANDS/SEGS	64 %
LYMPHOCYTES	26 %
MONOCYTES	7 %
EOSINOPHILS	0 %
BASOPHILS	0 %

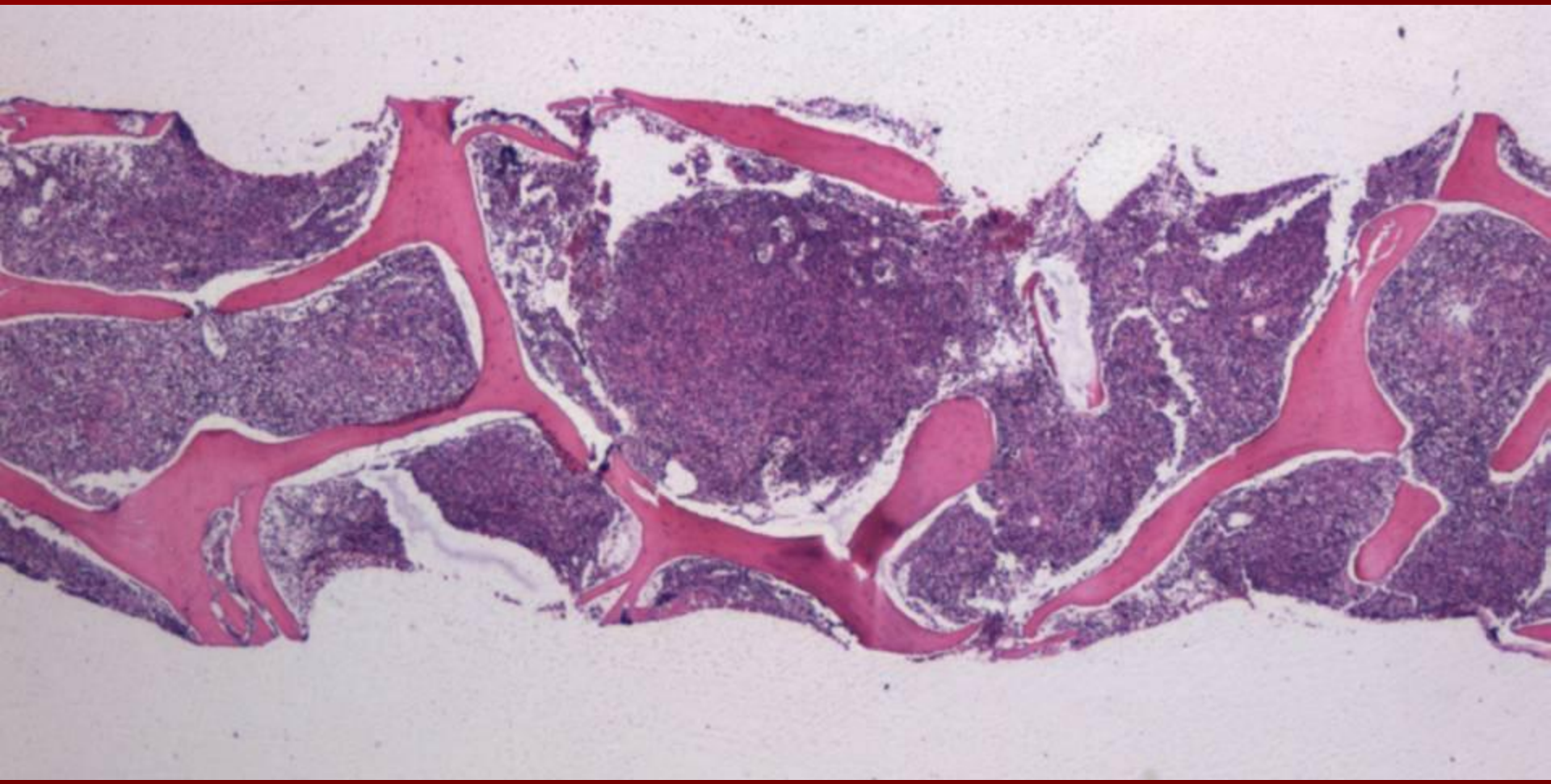
Aspirate smear

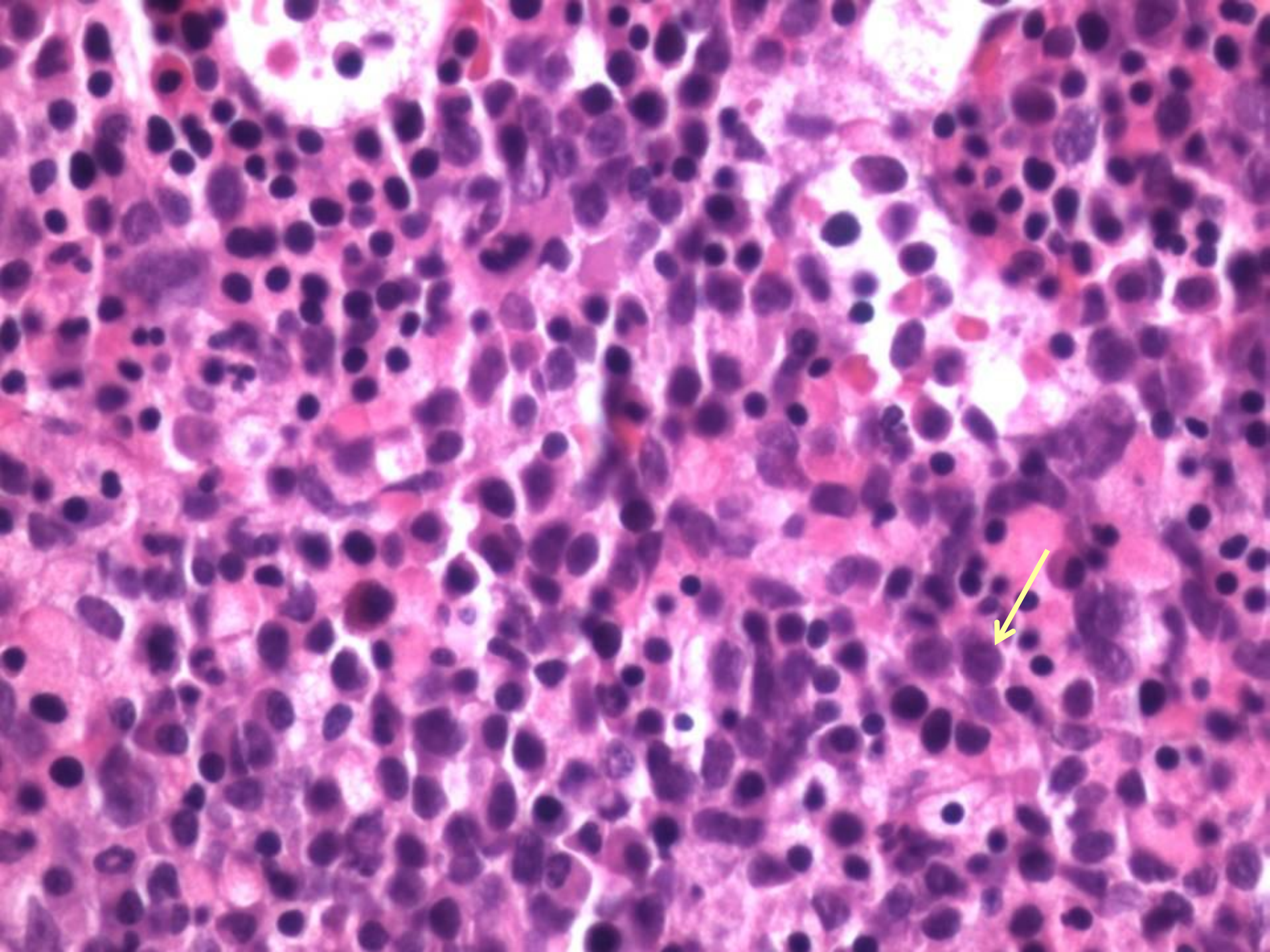





Immature cells

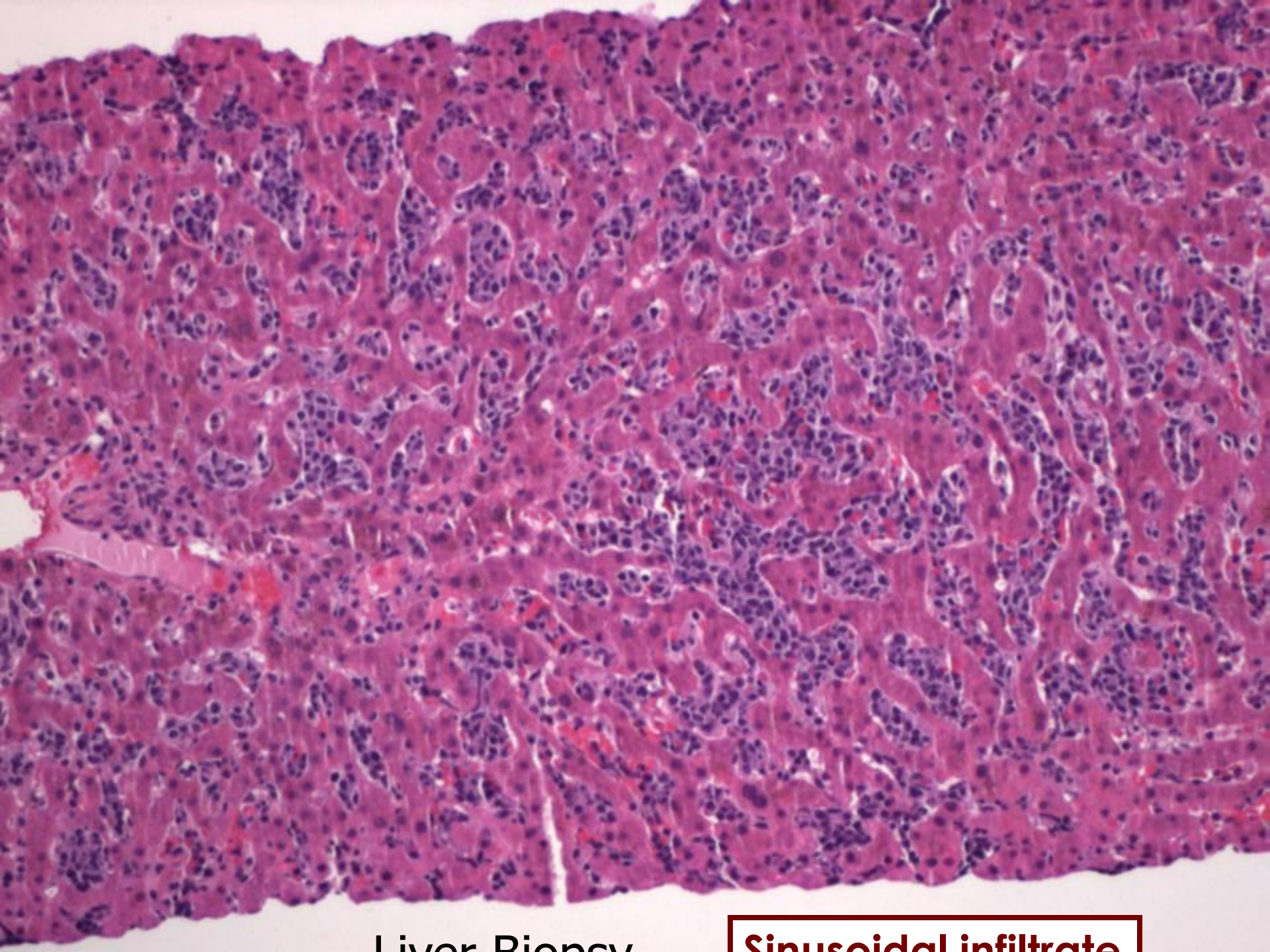
Bone Marrow core biopsy





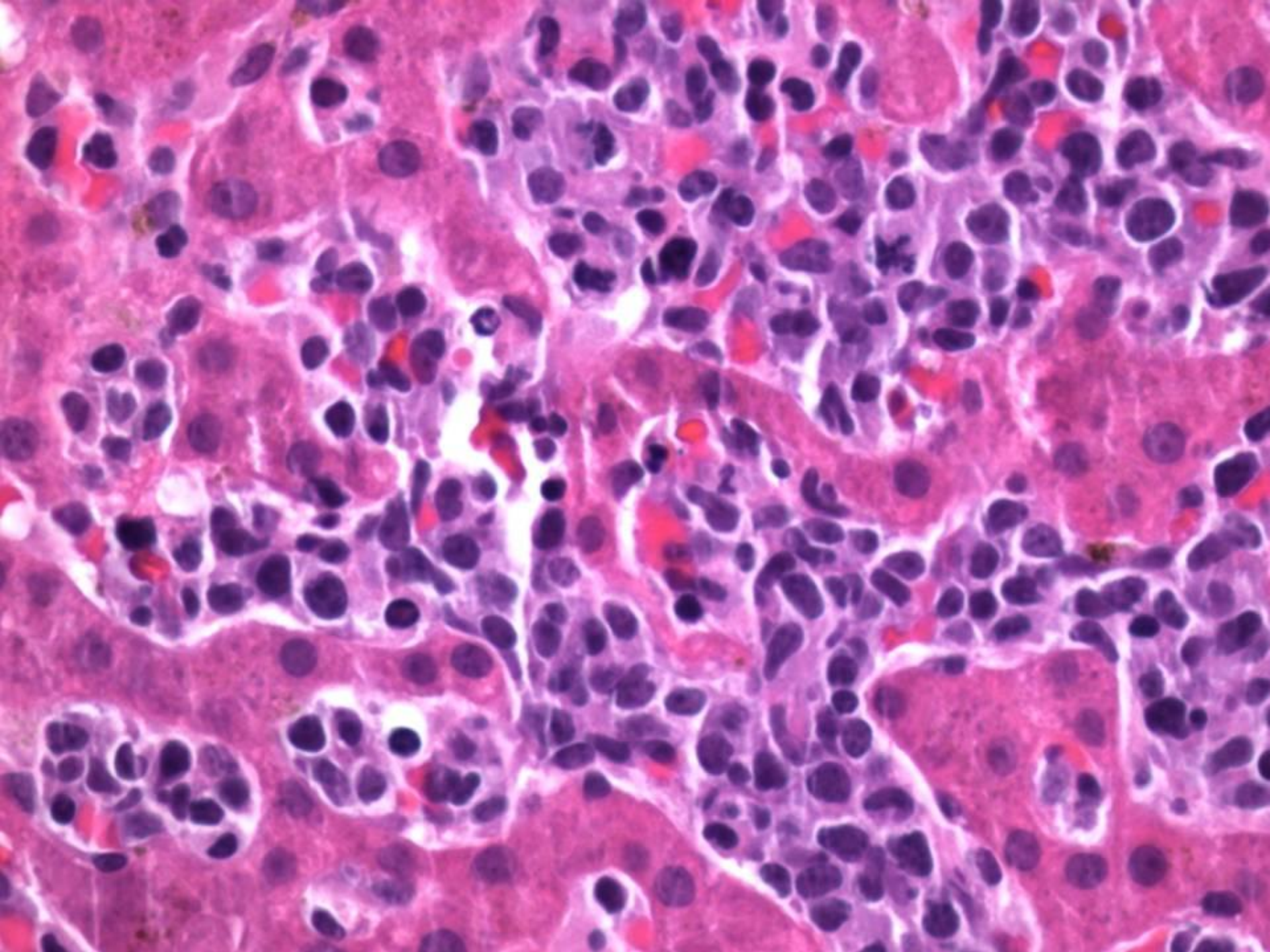
BM flow Data

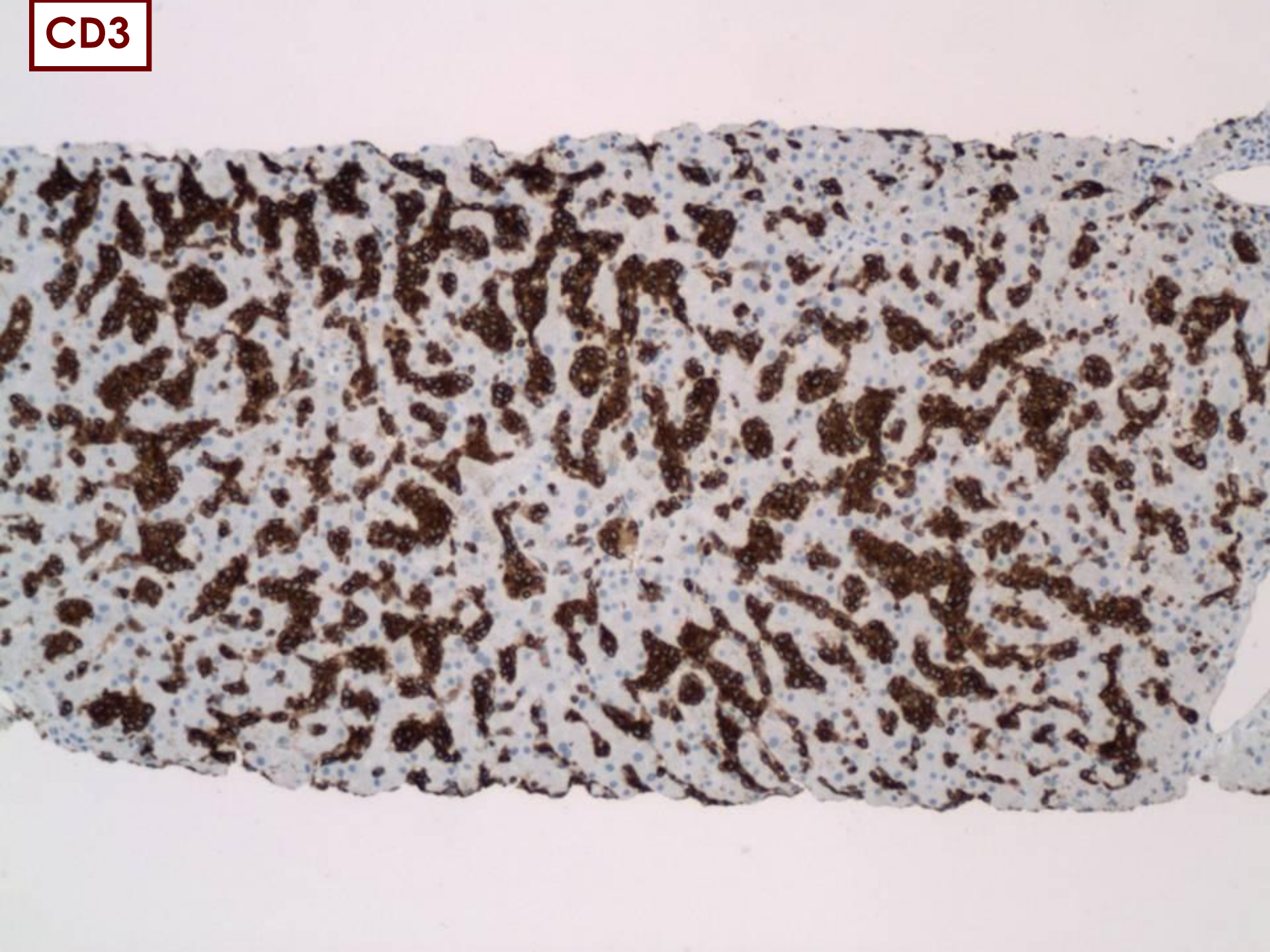
- T-cells: 25%
  - 20% abnormal
    - (+) CD3
    - (+) CD7
    - (+) CD56
    - (-) CD5
    - (-) CD4
    - (-) CD8
  - 5% normal



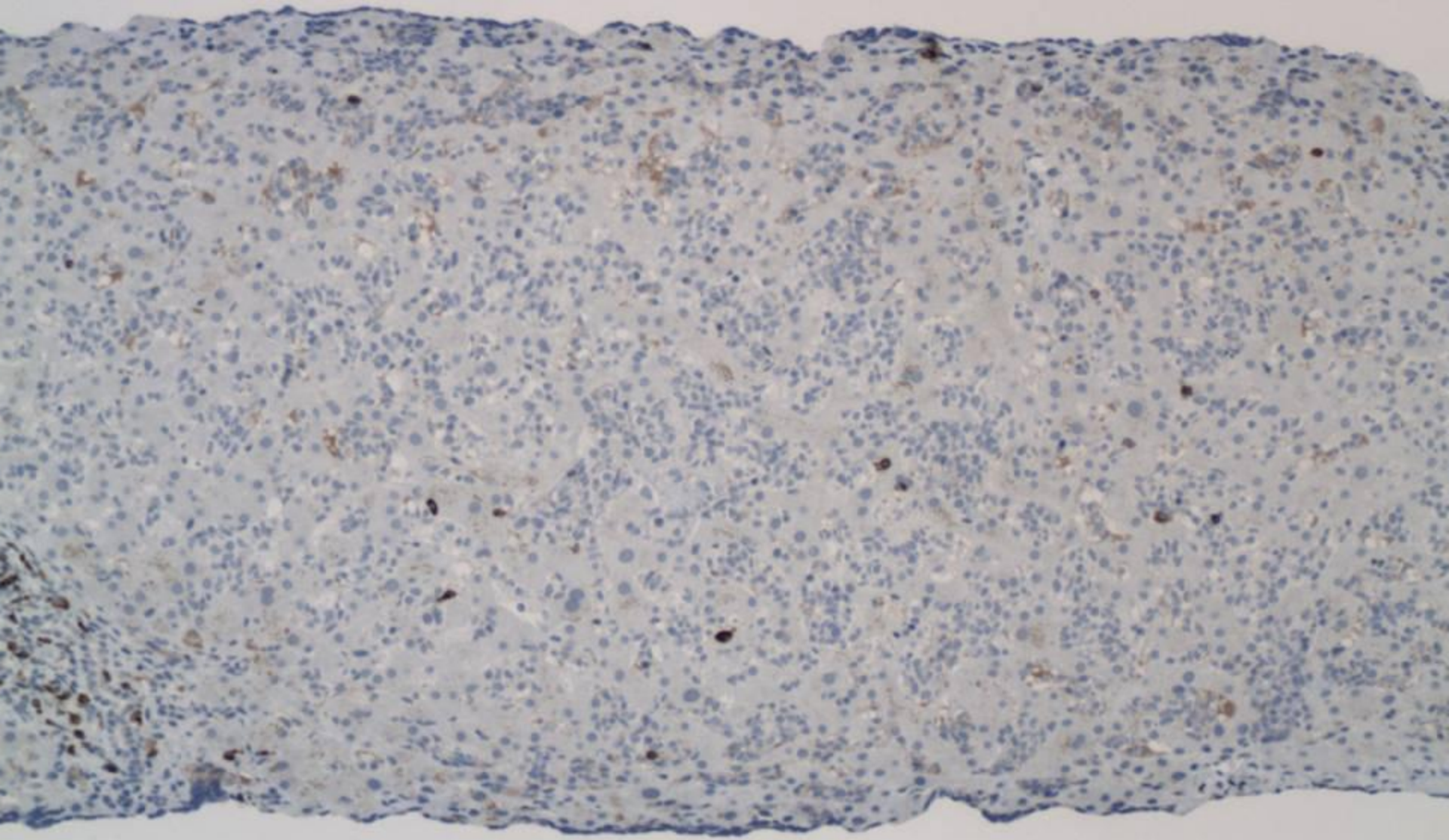
Liver Biopsy

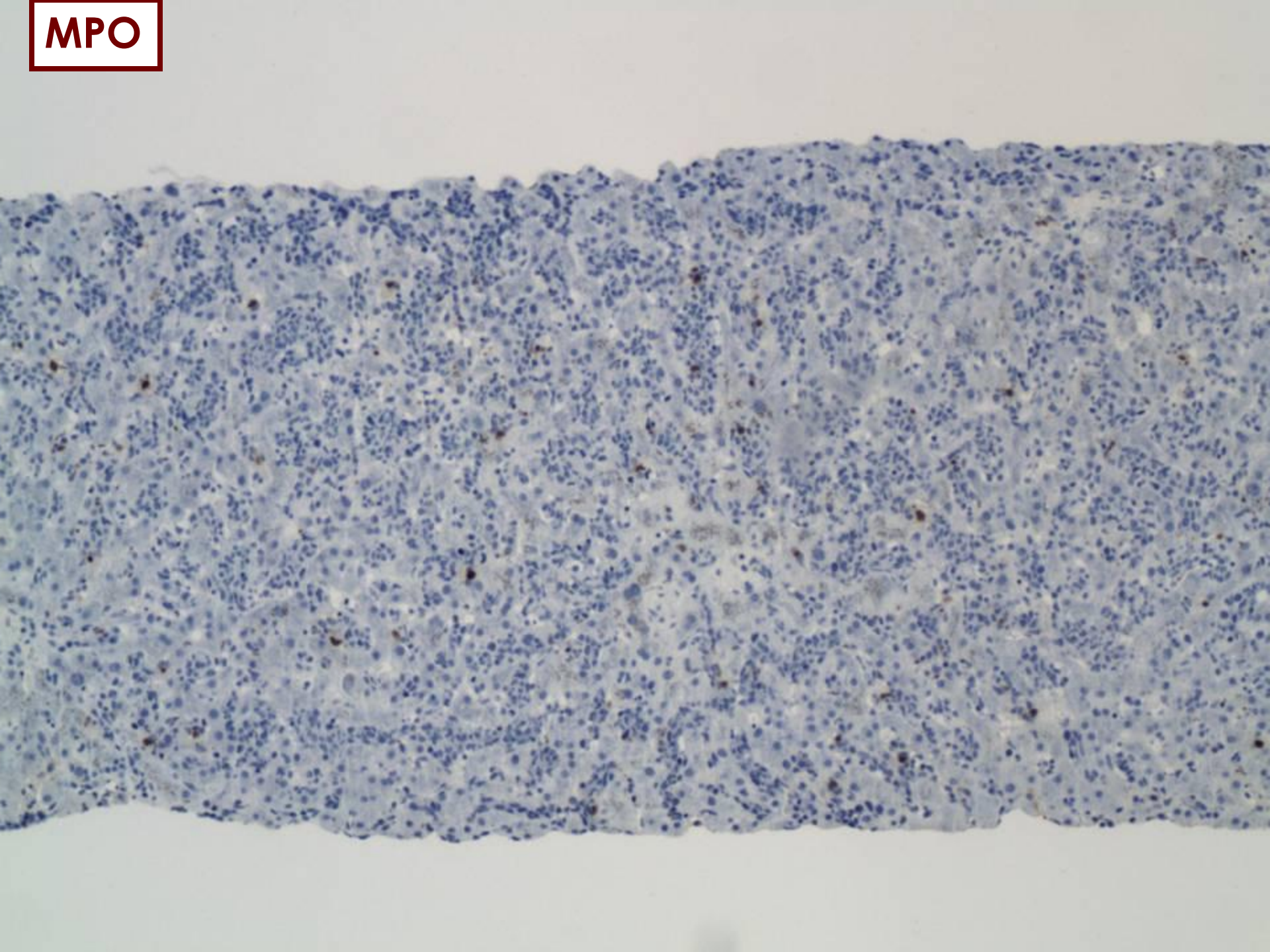
Sinusoidal infiltrate

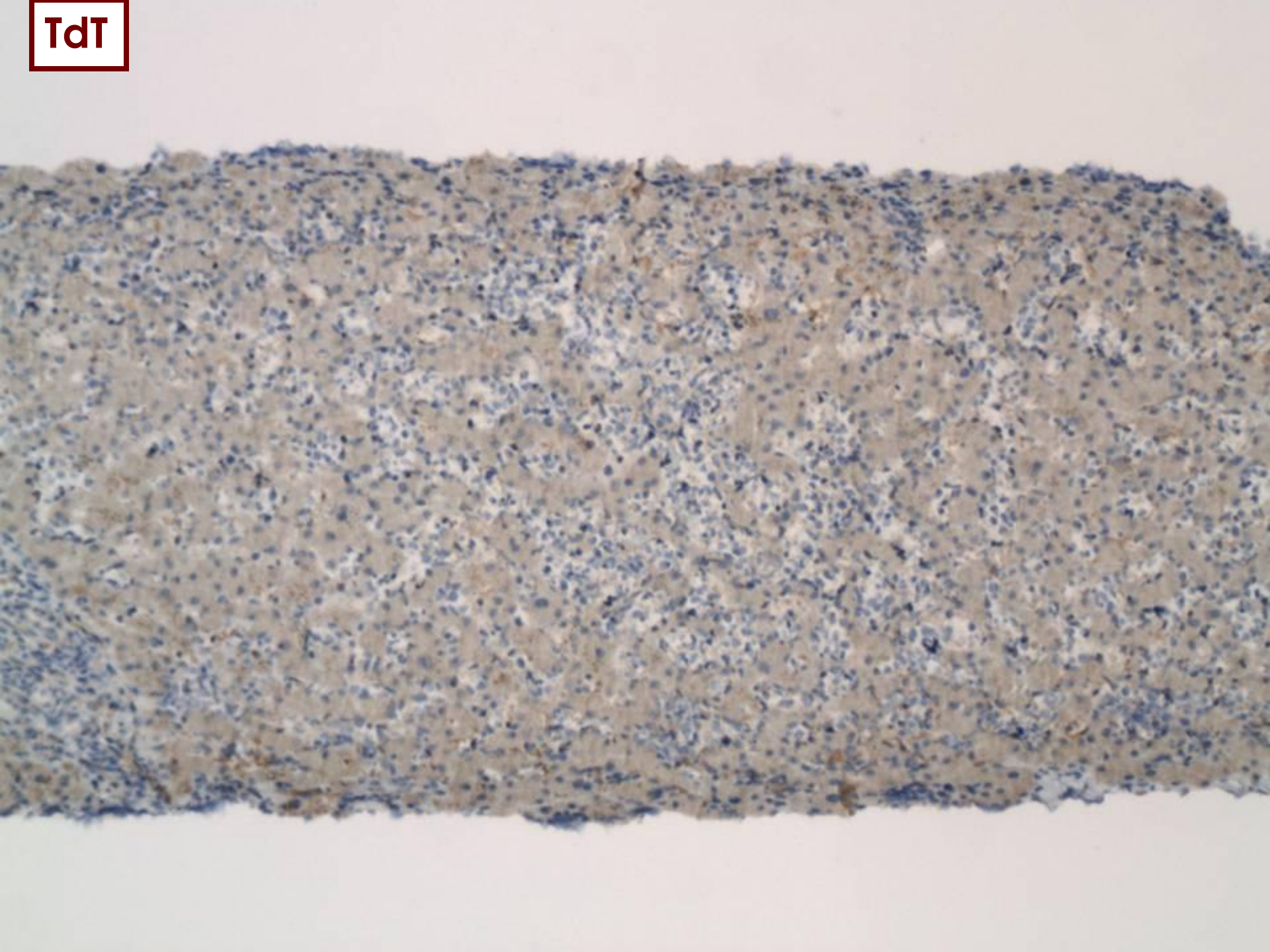



CD3

CD79/B-cell marker




MPO


TdT

Liver biopsy

- IHC

  (+) CD3 (-) CD20
  (-) TdT
  (-) MPO

- Flow cytometry

  30% of all cells are T-cells
  (+) CD3 (-) CD5
  (+) CD7 (-) CD4
  (+) CD56 (-) CD8

Diagnosis

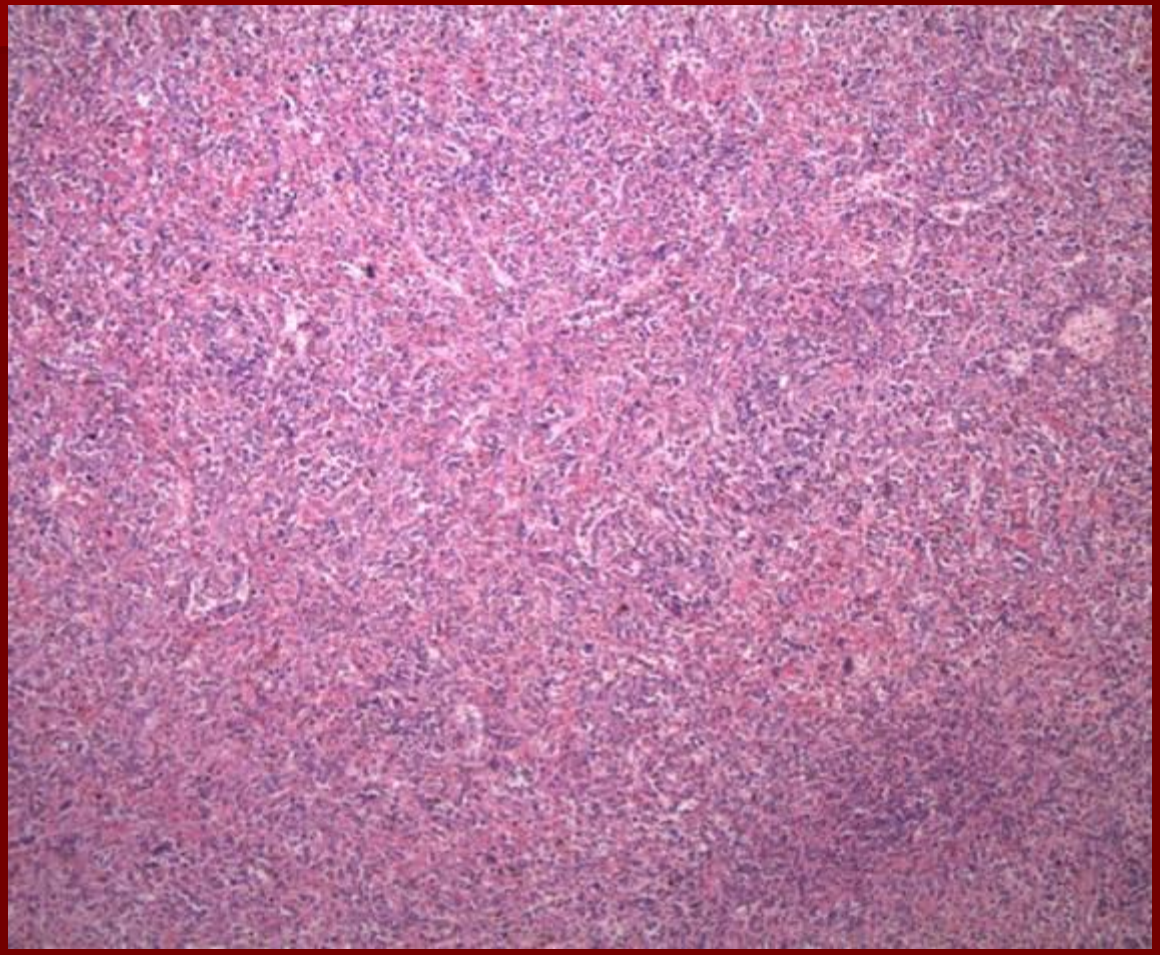
- Hepatosplenic T cell lymphoma
  (with significant autoimmune hemolysis)

Case 2: patient VC

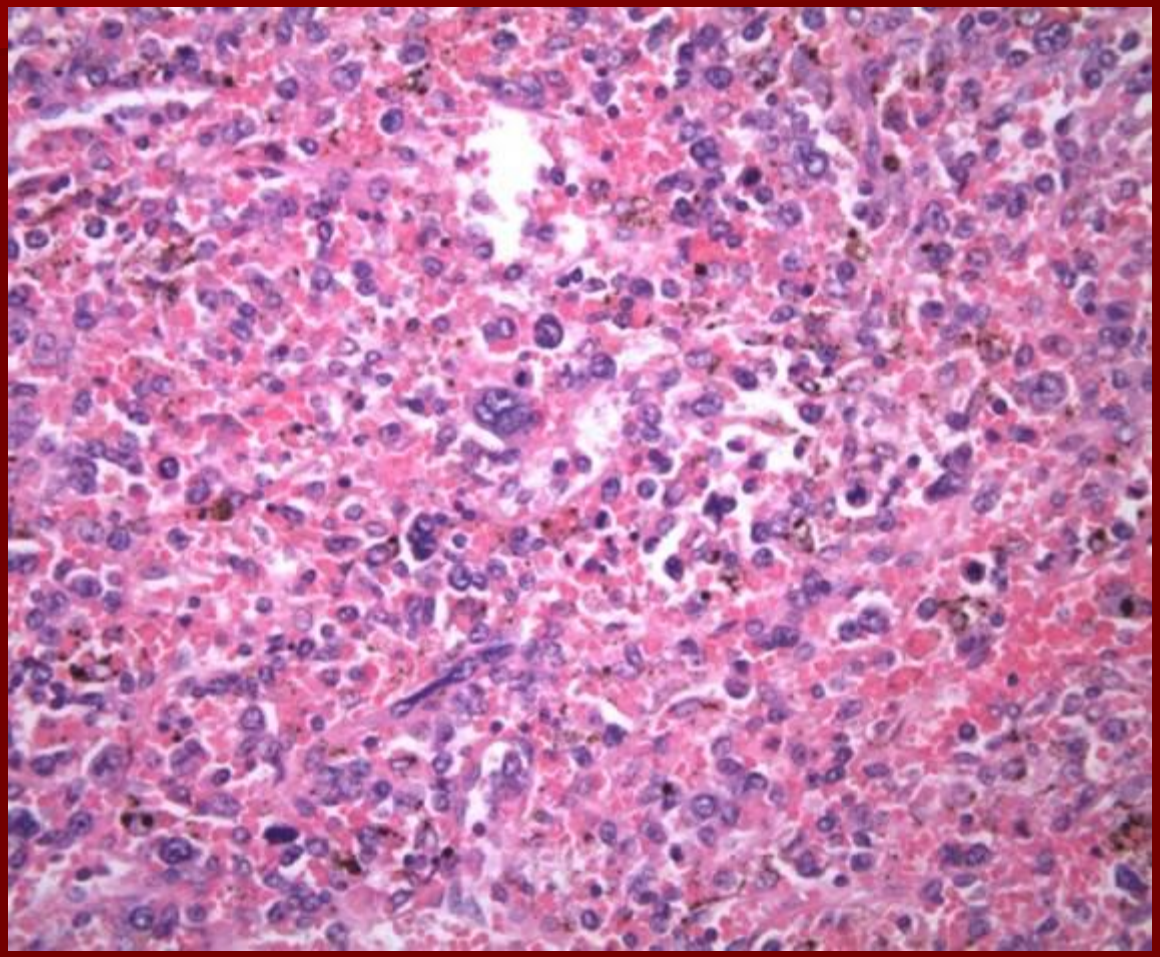
Clinical History

- A 42 year-old Hispanic man with a history of hemophagocytis (diagnosed with bone marrow), responded to therapy, now with recurrent hemophagocytosis and splenomegaly.
- Splenectomy was performed (2,050 gm)

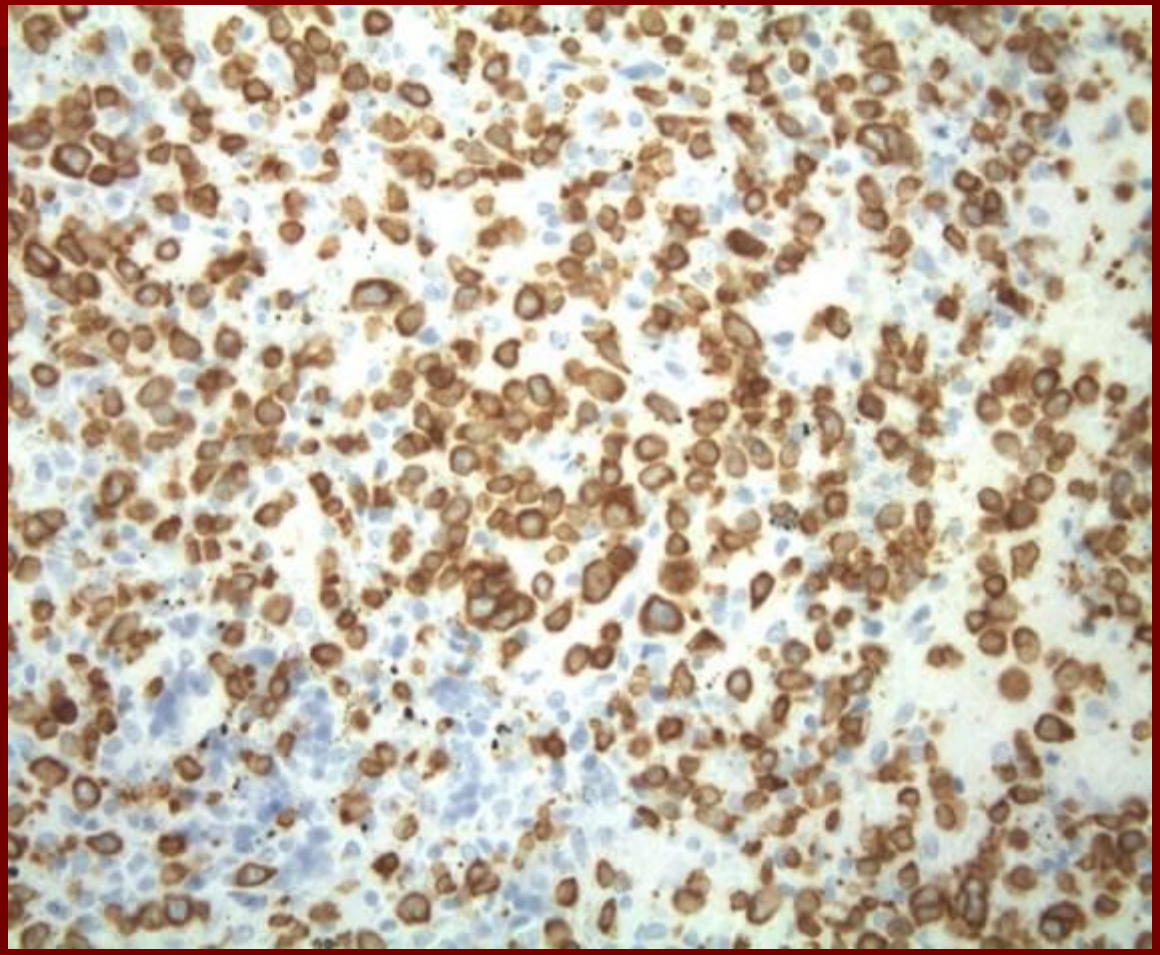
Spleen:H&E, 10x



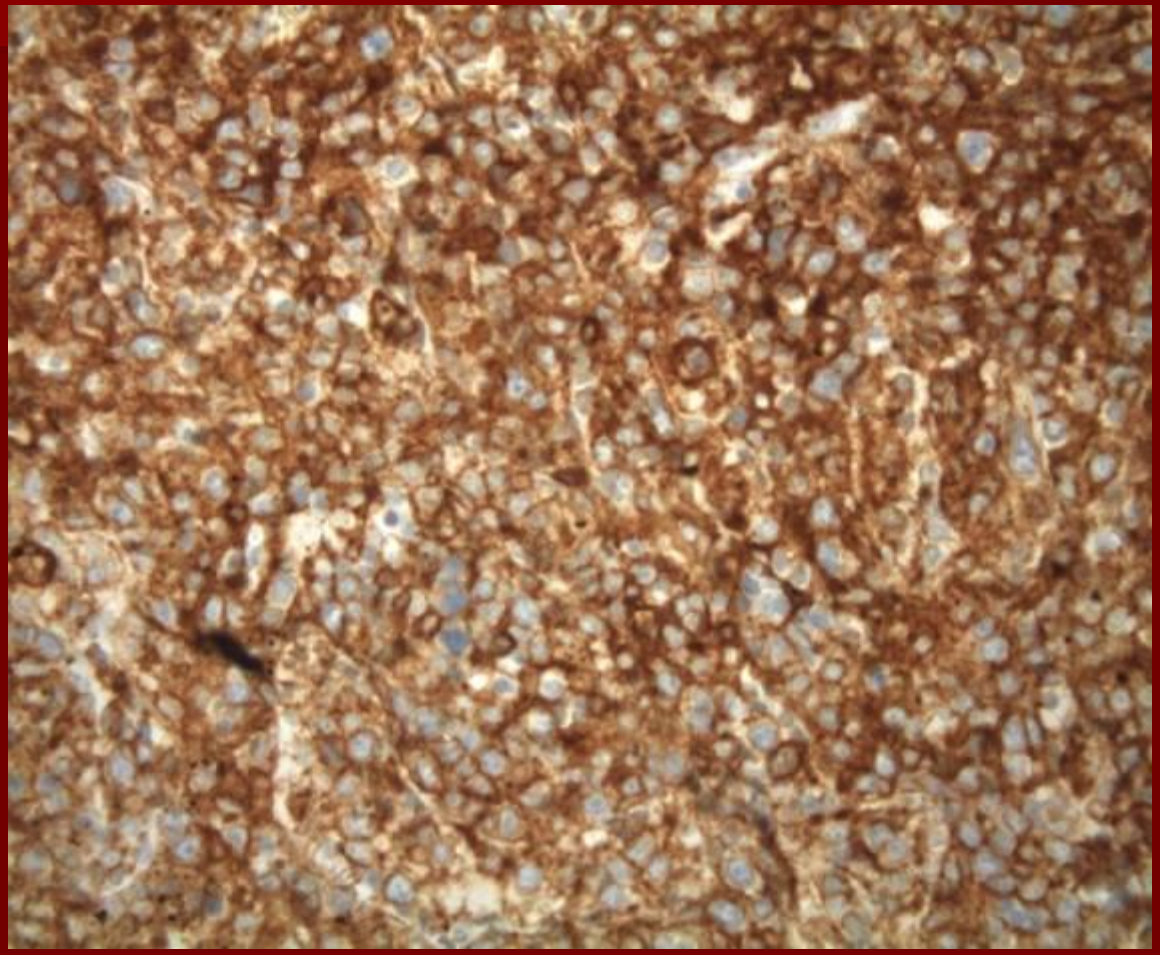
Spleen:H&E, 40x



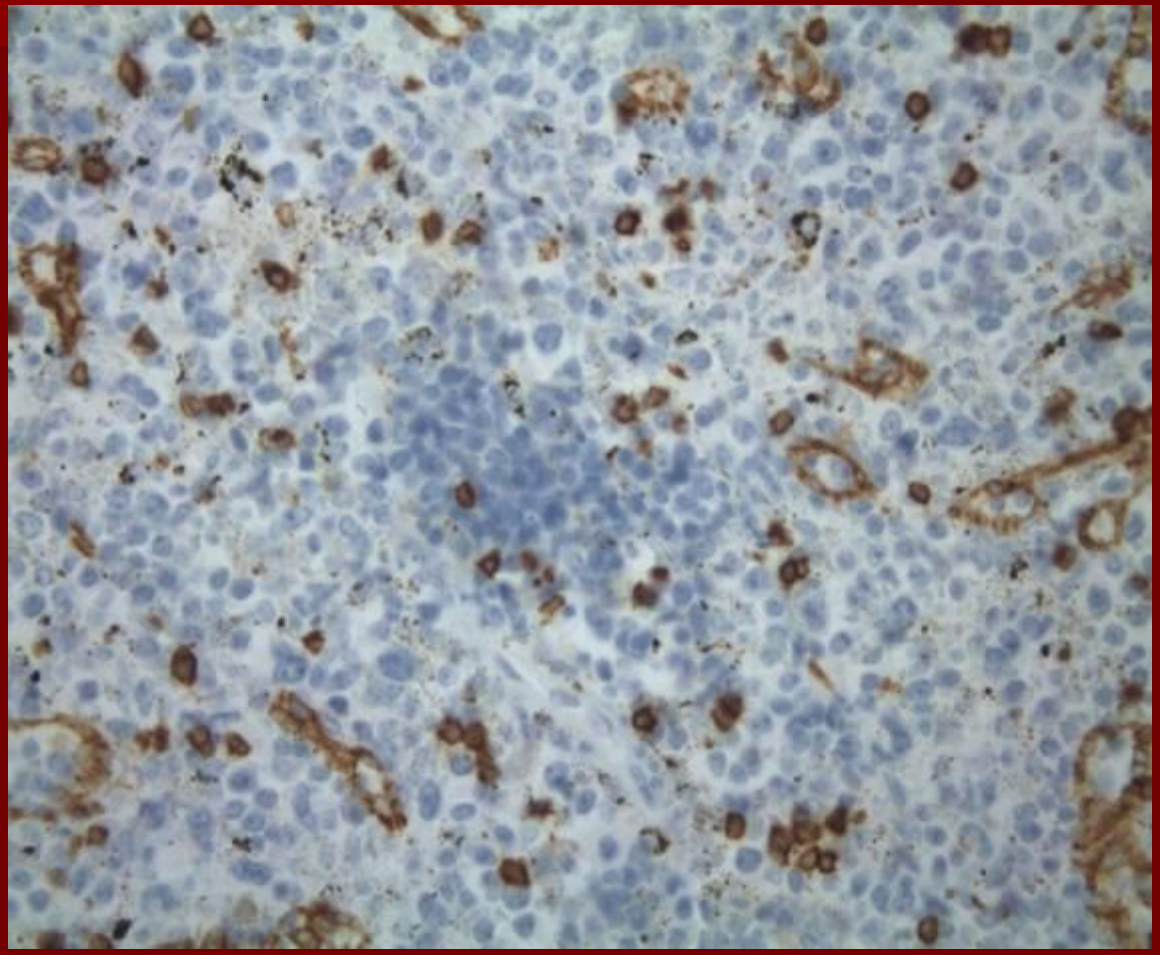
Spleen:CD3, 40x



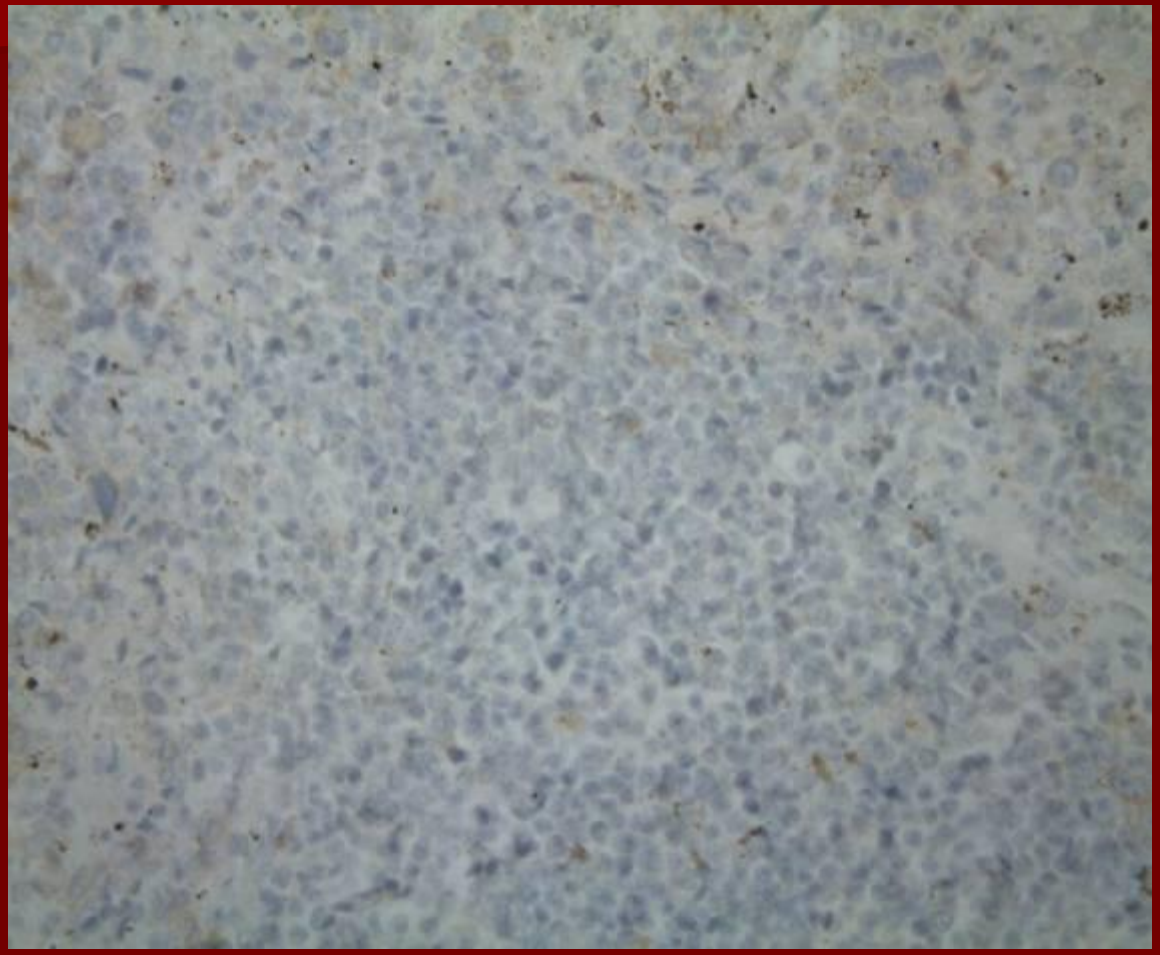
Spleen:CD4, 40x



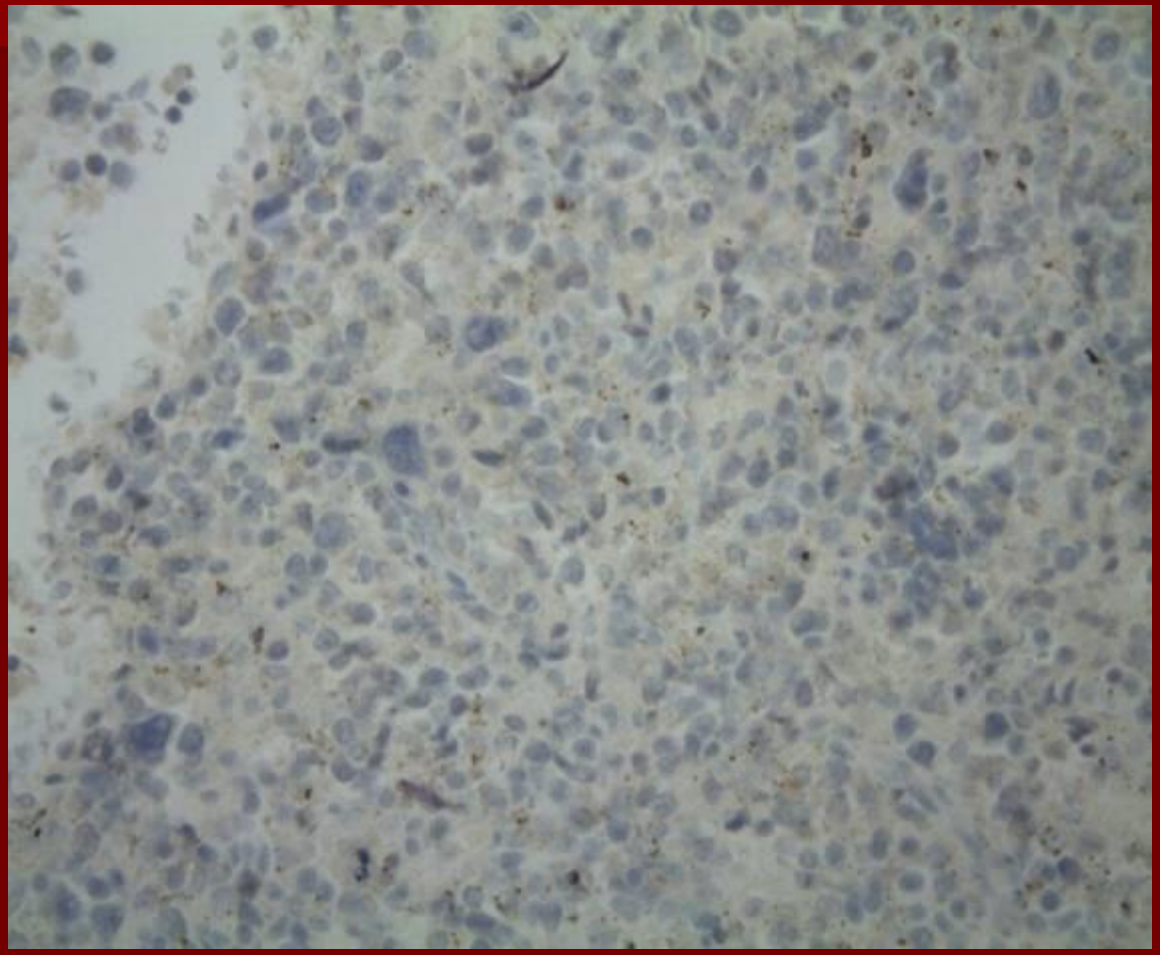
Spleen:CD8, 40x



Spleen:CD30, 40x



Spleen: ALK-1, 40x



Diagnosis

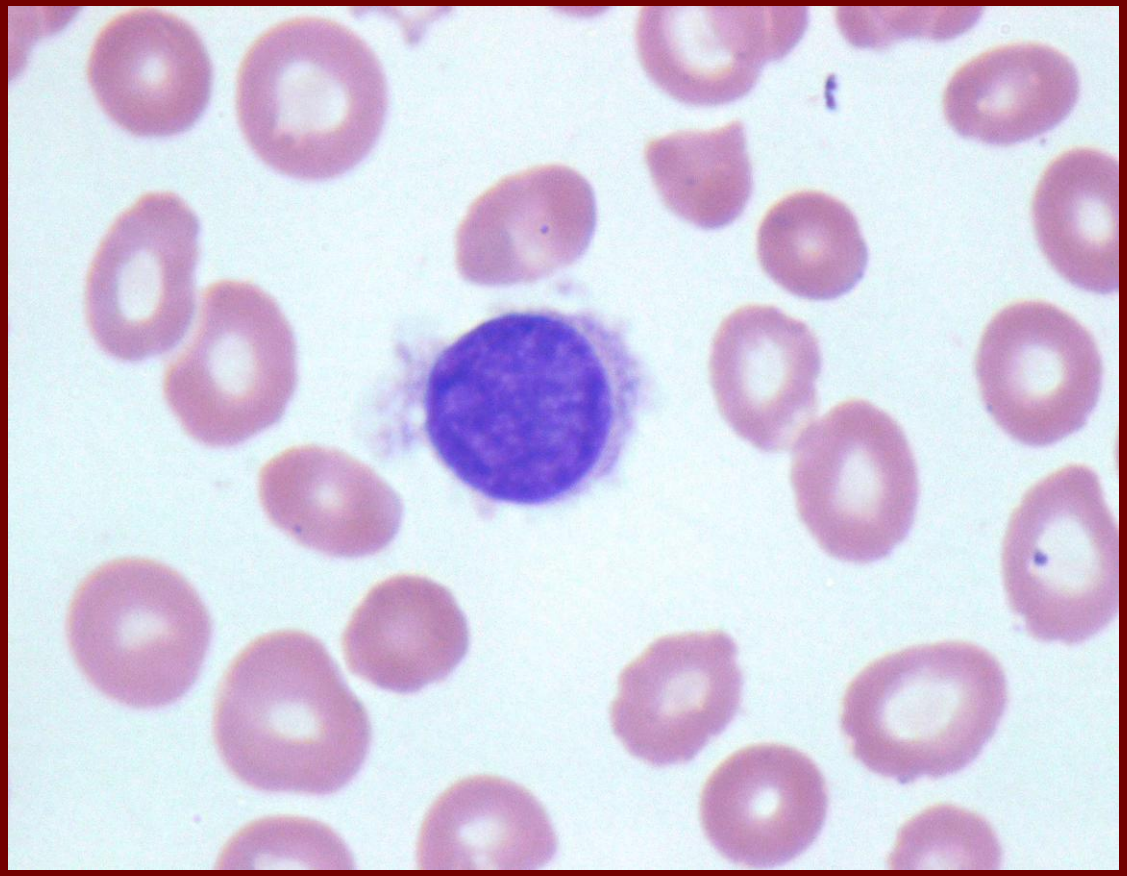
- Peripheral T cell lymphoma, NOS

Case 3: patient JB

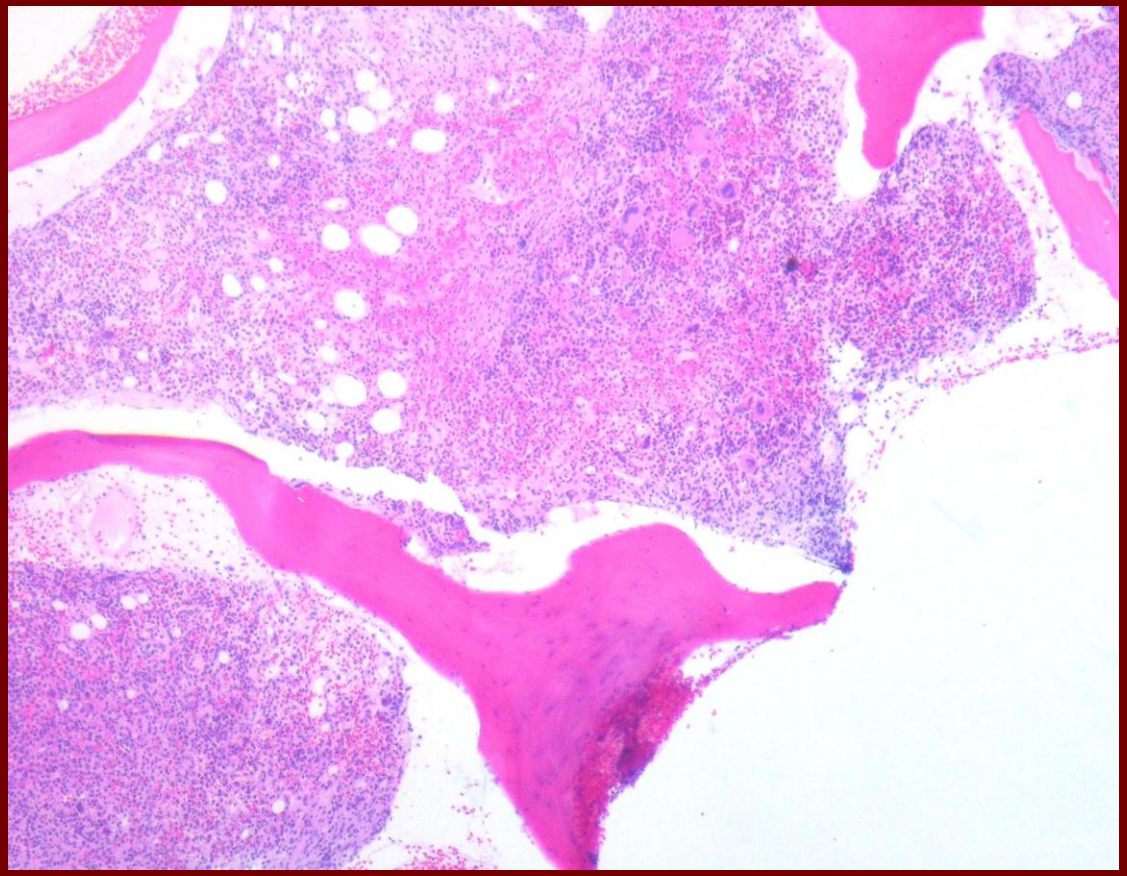
Bone Marrow Case

- 49 year old white male with abdominal distension x 6 months, found to have splenomegaly, and pancytopenia. No lymphadenopathy is noted.
- WBC=2.6, Hgb=5.5, Plt=16K, MCV=98.6, Retic 2.1%
  Lymph 68%, NRBC 3

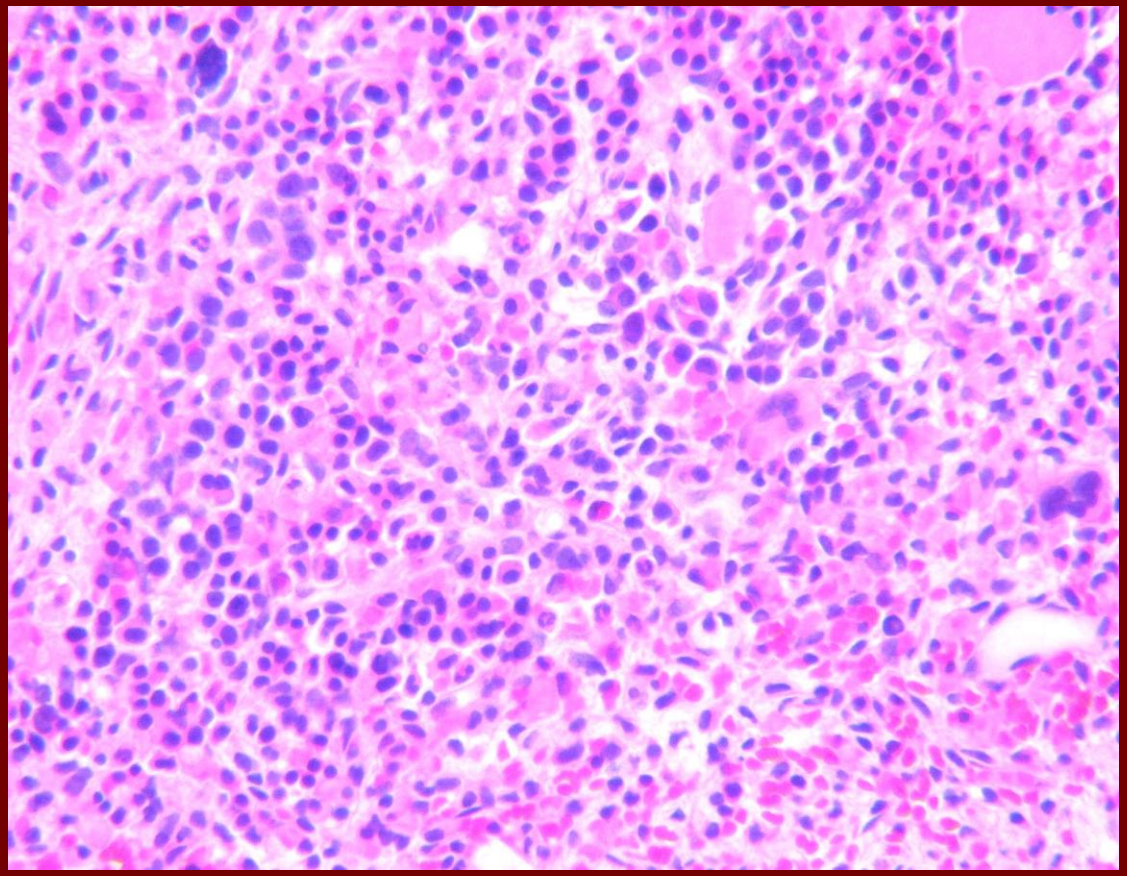
Peripheral Blood Smear



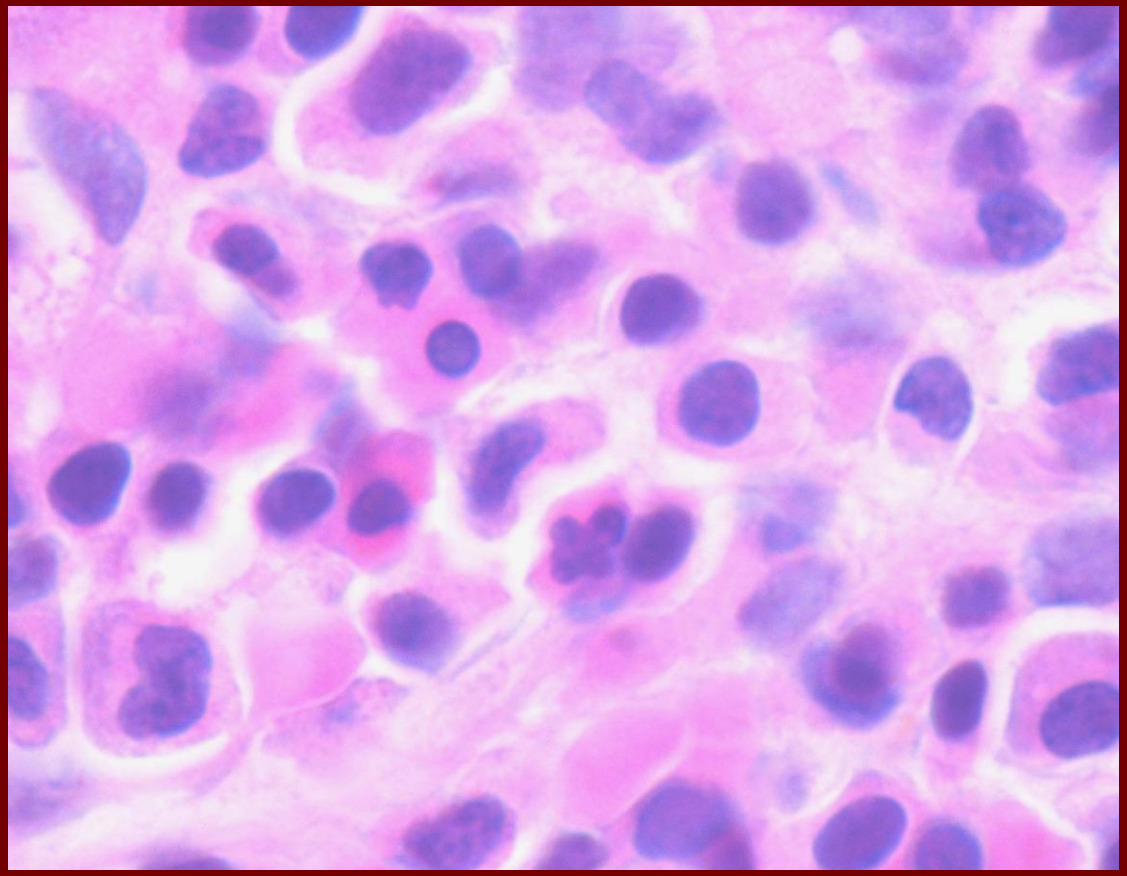
Bone Marrow Biopsy



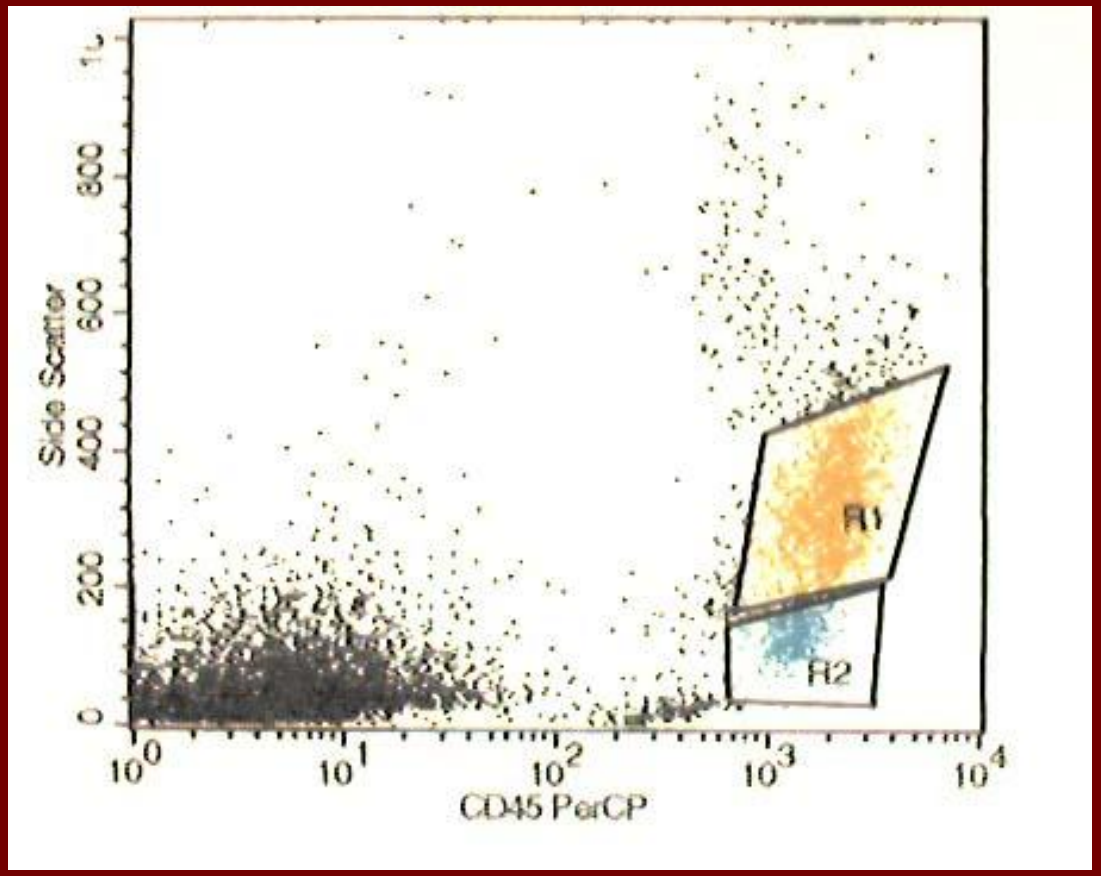
Bone Marrow Biopsy



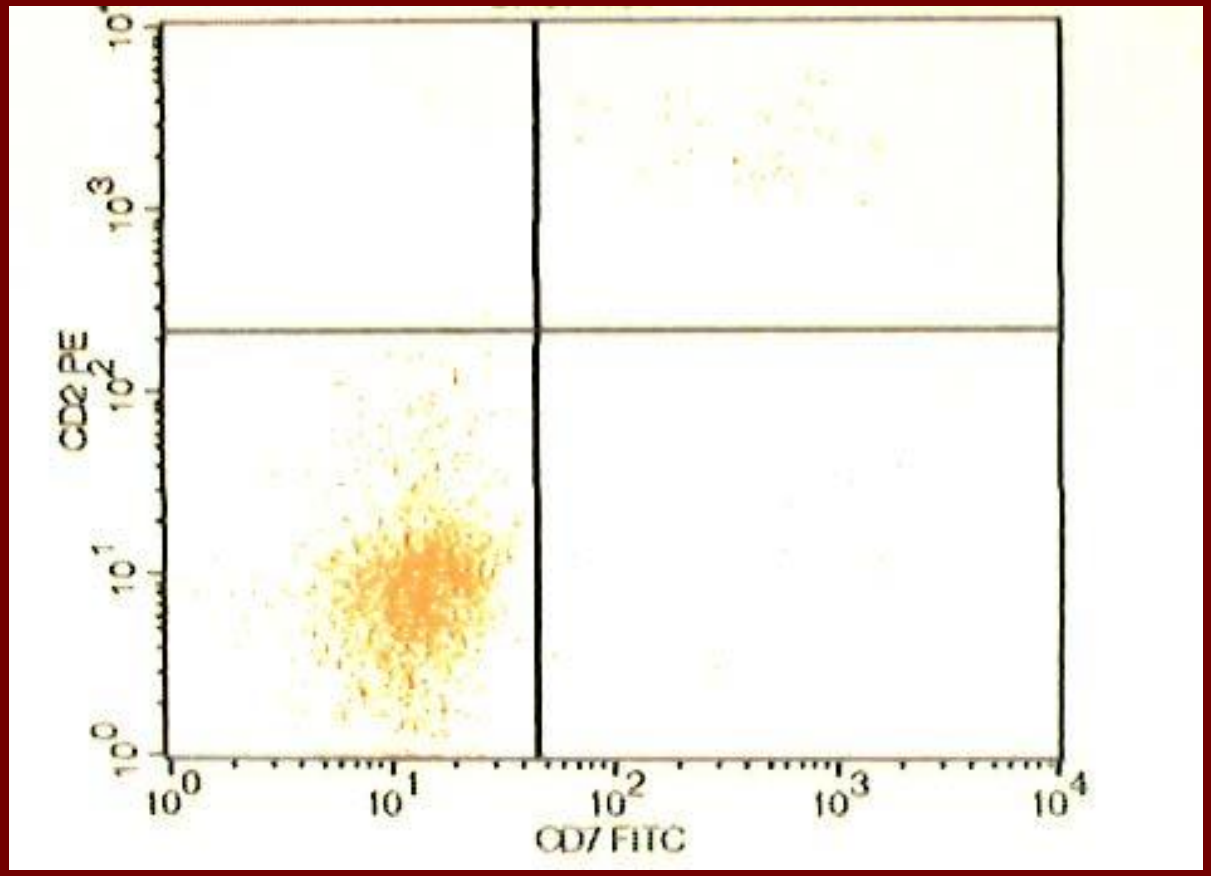
Bone Marrow Biopsy



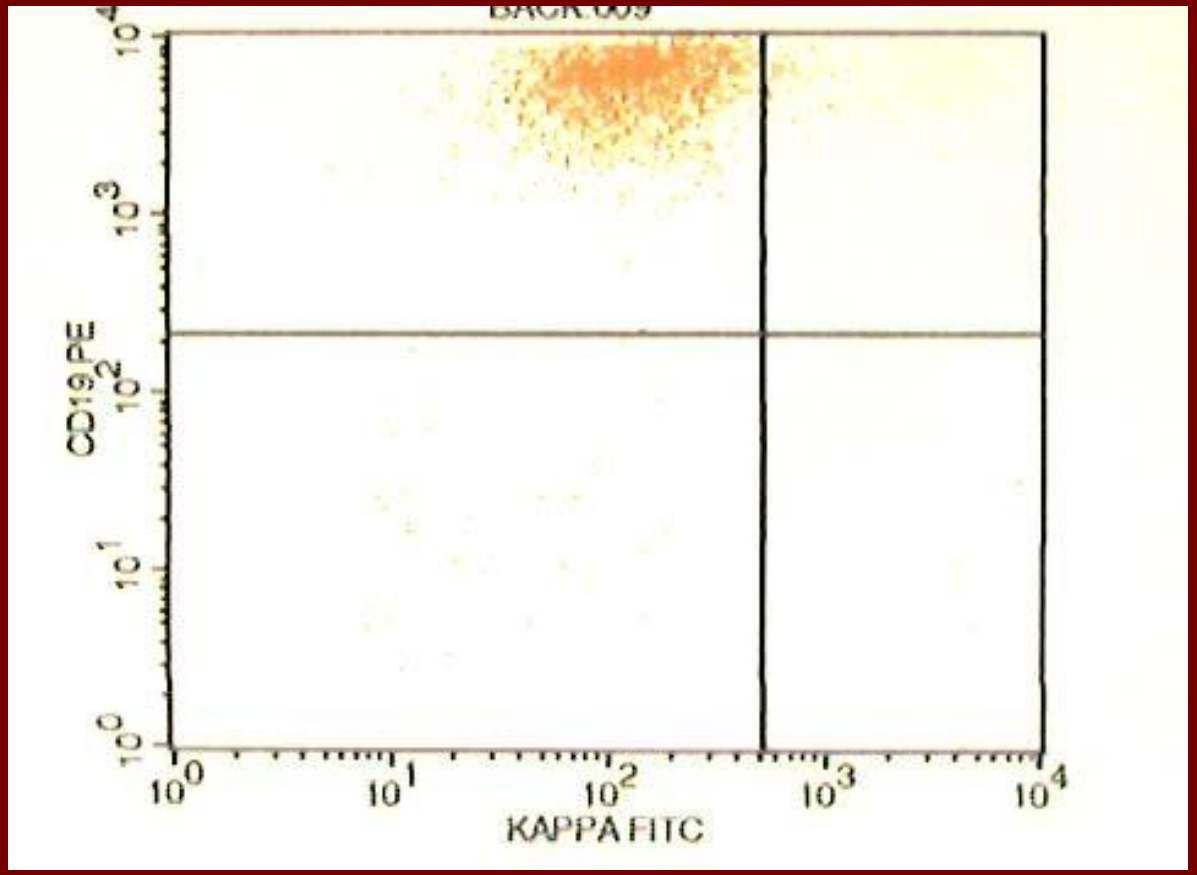
Flow Cytometry Study



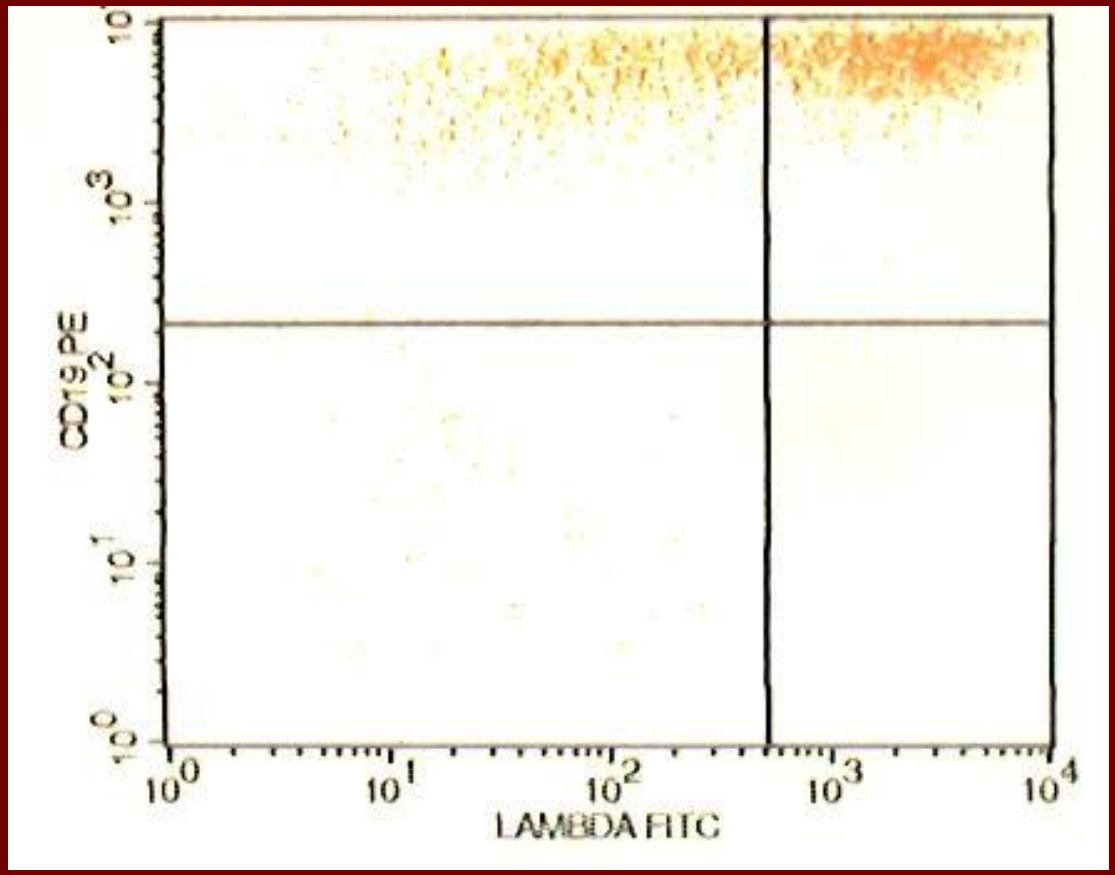
Flow Cytometry Study



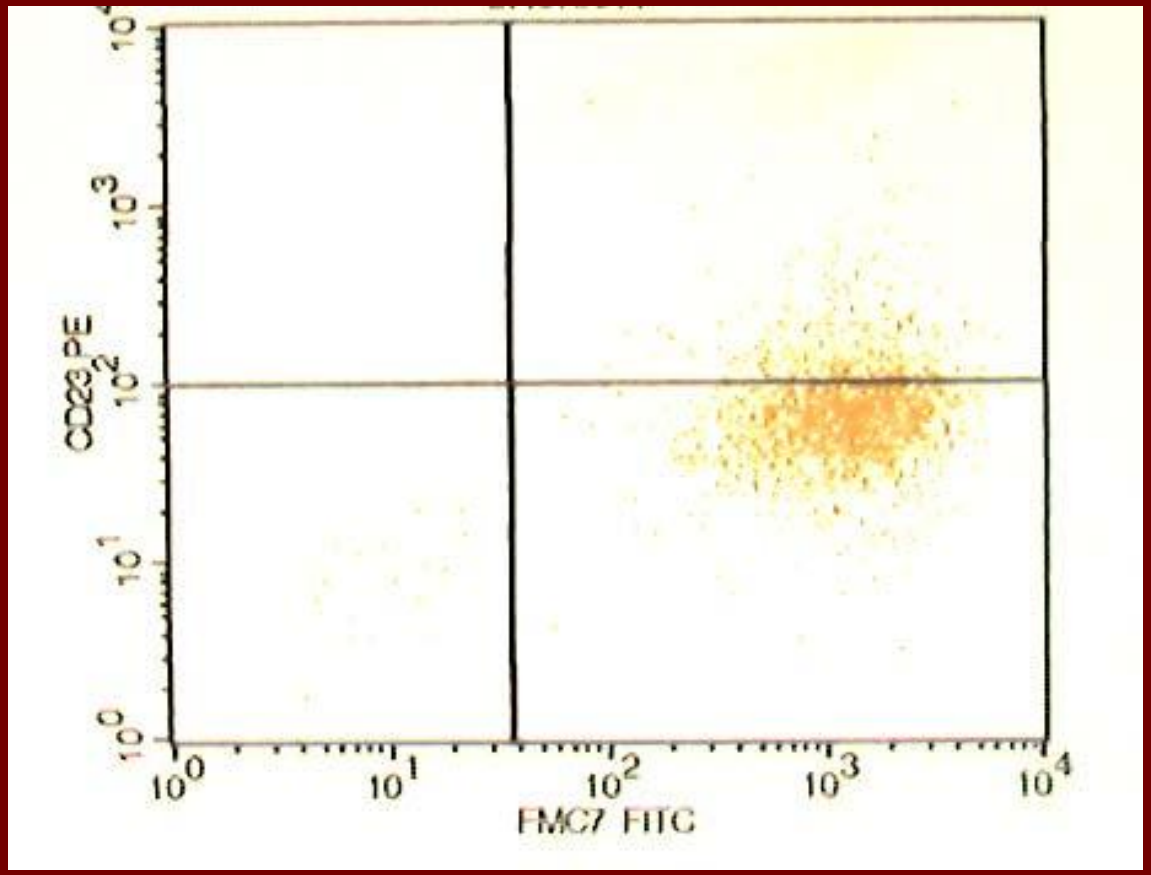
Flow Cytometry Study



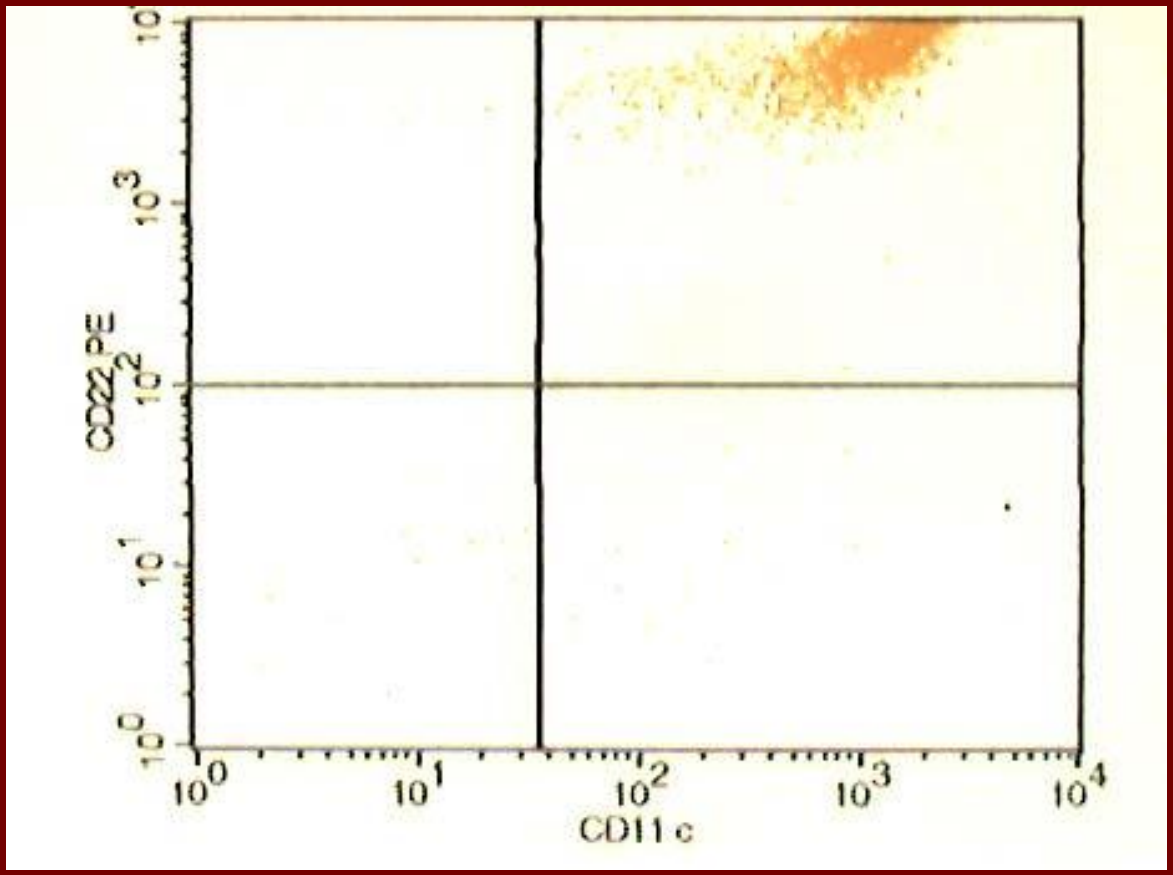
Flow Cytometry Study



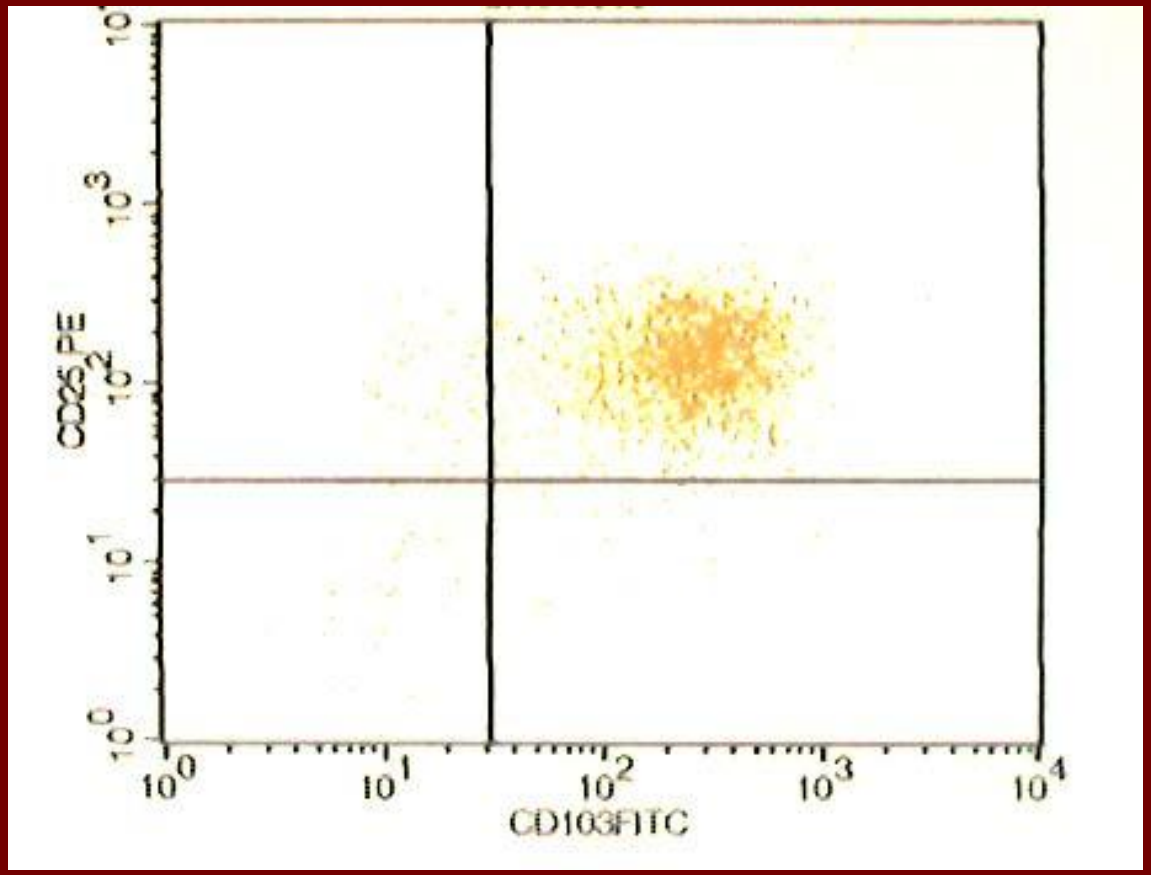
Flow Cytometry Study



Flow Cytometry Study



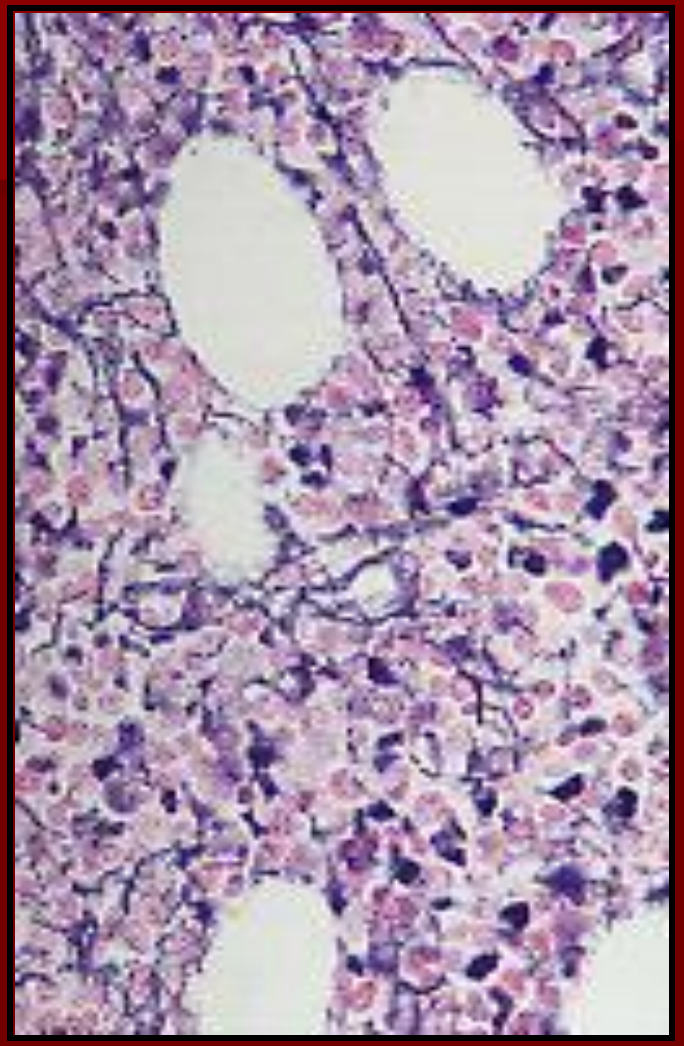
Flow Cytometry Study

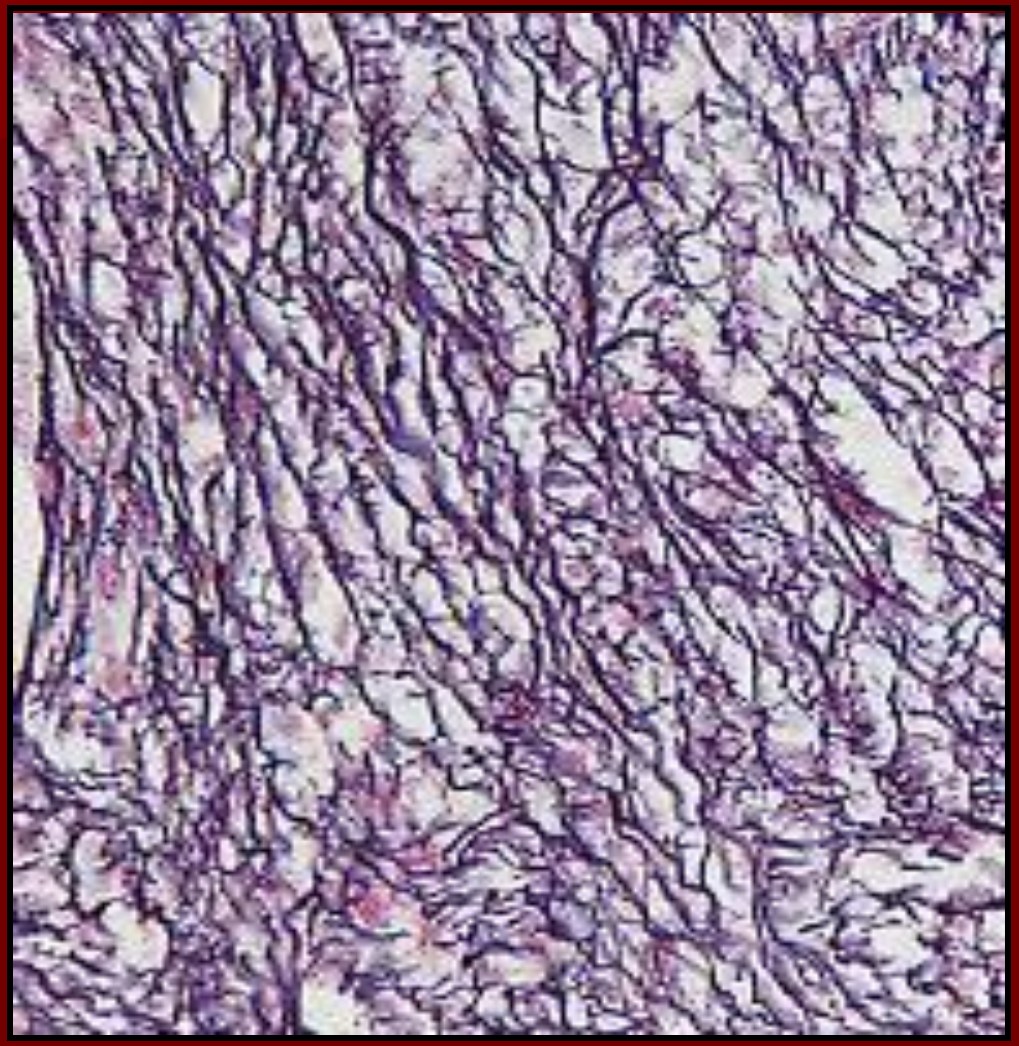


Diagnosis

- Flow cytometry :
  Lymphocytic subpopulation pos for CD19, CD20, CD22, CD11c, CD25, CD103, FMC7, Lambda light-chain restriction (strong intensity of CD22, CD11c)
- DX: hairy cell leukemia
- Tests not performed:
  - Tartrate resistant acid phosphotase (TRAP)
  - Reticulin stain
  - EM

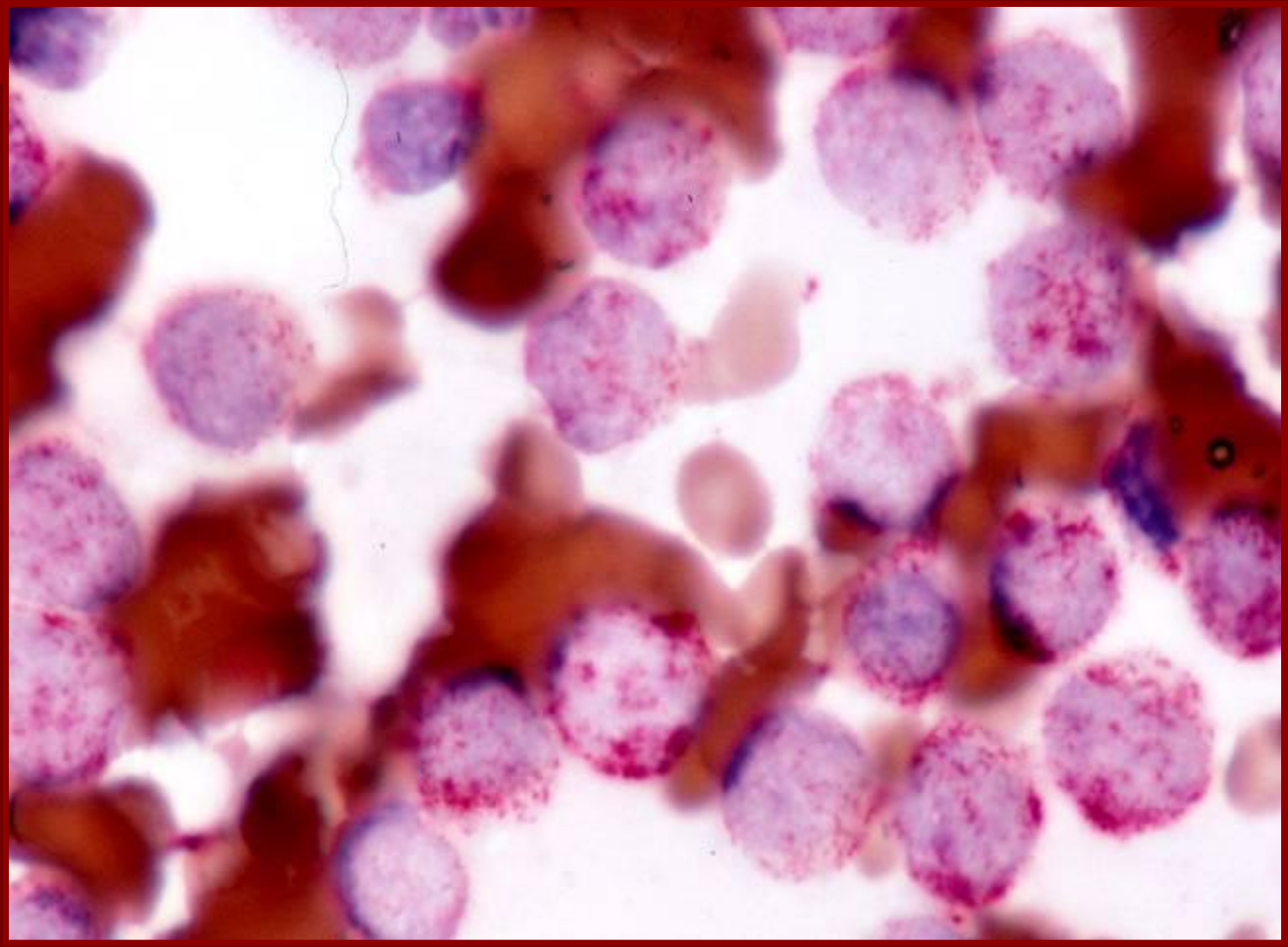
Hairy Cell Leukemia Bone marrow-Reticulin stain



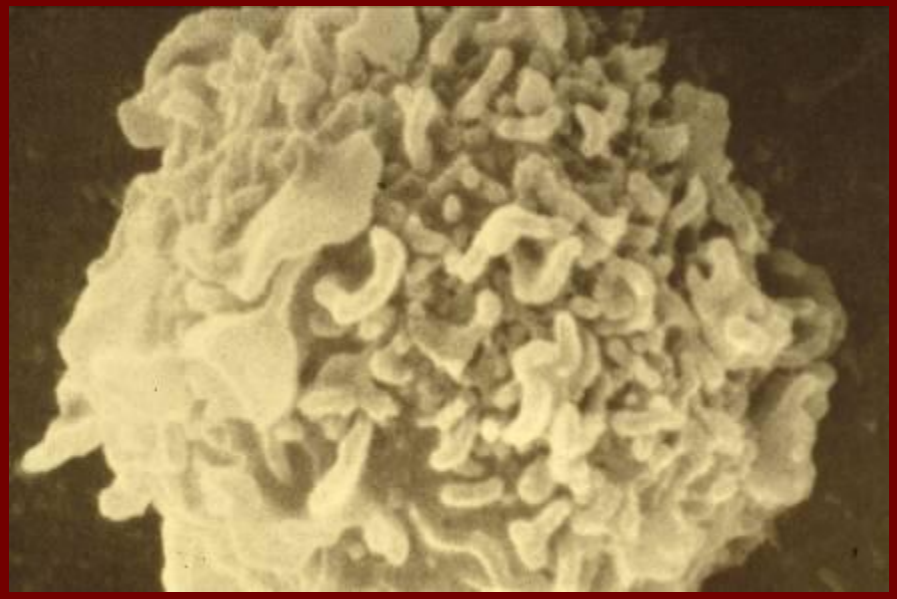


Hairy Cell Leukemia

TRAP stain

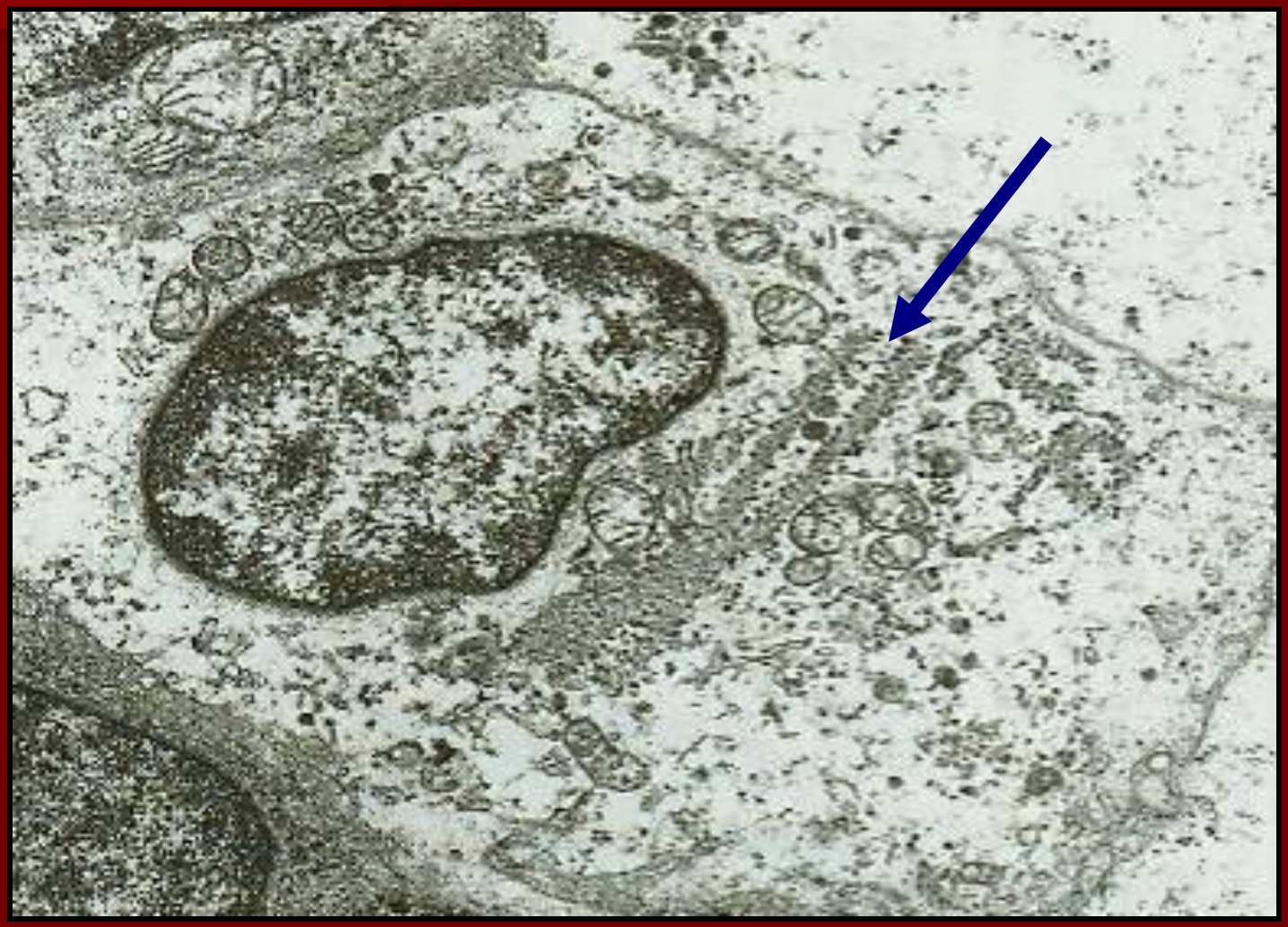


Hairy Cell Leukemia: scanning EM



Hairy Cell Leukemia: transmission EM

Ribosome lamellar complexes: double tubule structures composed of protein, unknown role in pathogenesis of HCL



Hairy Cell Leukemia
Morphology in Spleen, Liver, Lymph Node

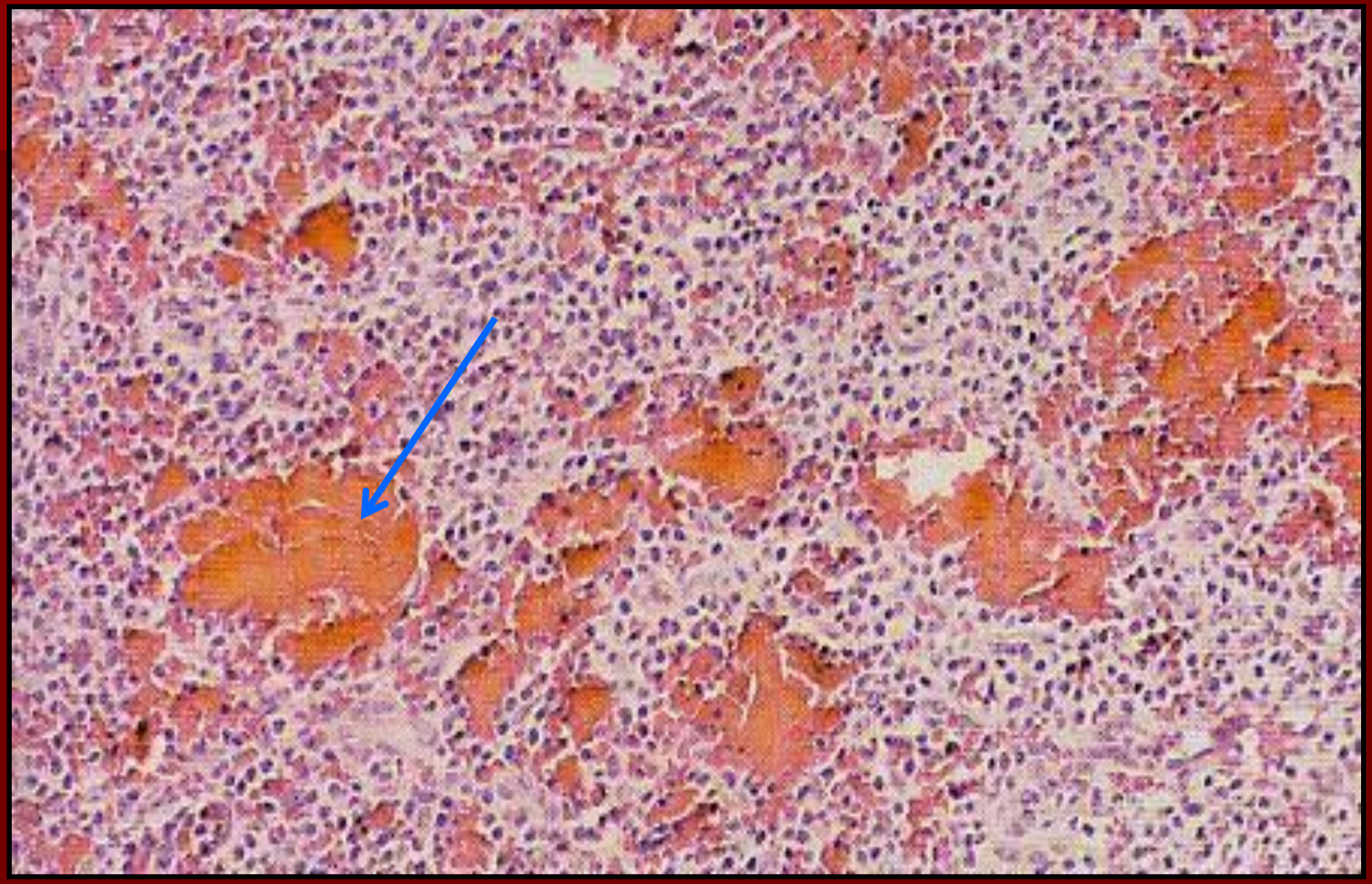
-Spleen:
  Infiltrate red pulp cord
  White pulp atrophic
  RBC lakes
-Liver: sinusoidal and portal infiltrates
-LN: paracortical, sparing of follicles

Hairy Cell Leukemia

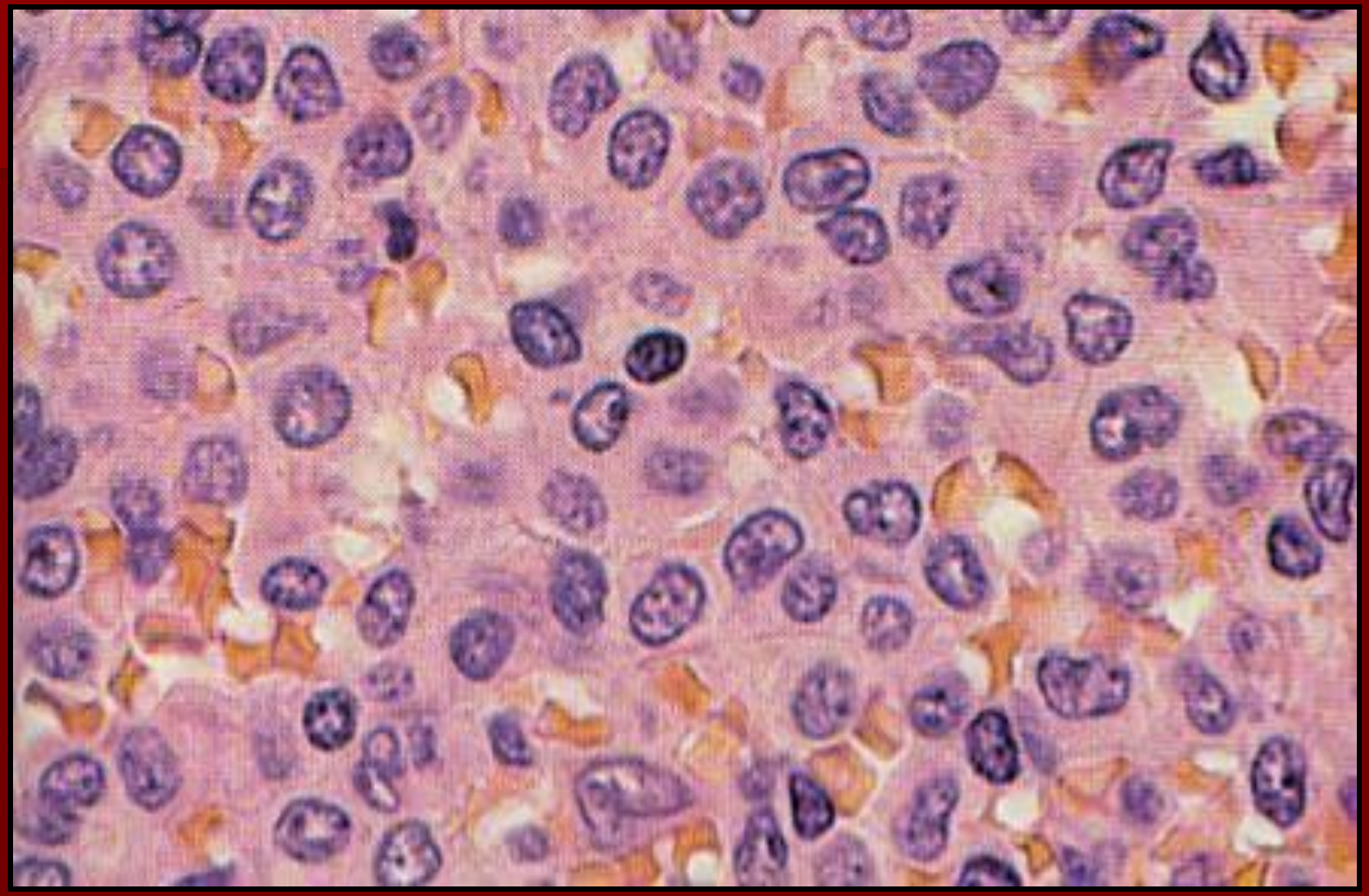
Spleen

Hairy Cell Leukemia

Spleen: red cell lakes



Hairy Cell Leukemia: Spleen



Hairy Cell Leukemia: Liver