University of Baghdad
College of Medicine
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Title: WBC Disorders – Part 2A

Grade: 4

Module: PATHOLOGY (Hematology)

Speaker: Professor Dr. Haithem Ahmed Al-Rubaie

Date: 24 Oct – 8 Nov 2023

WBC Disorders (Part 2A)

Chronic Lymphoid Leukemia

Learning Objectives:

By the end of this session the student should be able to:

1. Diagnose chronic lymphocytic leukemia (CLL).
2. Describe the laboratory findings in CLL.
3. Describe the laboratory findings in hairy cell leukemia.

CHRONIC LYMPHOID LEUKEMIAS (Lymphoproliferative Disorders)

A number of disorders are included in this group characterized by accumulation in the blood of mature lymphocytes of either B- or T-cell type.

Chronic Lymphocytic Leukemia

CLL is the most common of the chronic lymphoproliferative disorders (LPDs) accounting for 60% of cases, and it is the most common in the West representing about 25% of all leukemias in adults > 50 years

There is 7-fold increased risk of CLL in the close relatives of the patient

CLL is rare in the Far East

Definition

CLL is a chronic B-cell LPD characterized by the accumulation of small mature looking monoclonal neoplastic B-lymphocytes in the PB, BM and secondary lymphoid tissues (LNs, spleen and liver).

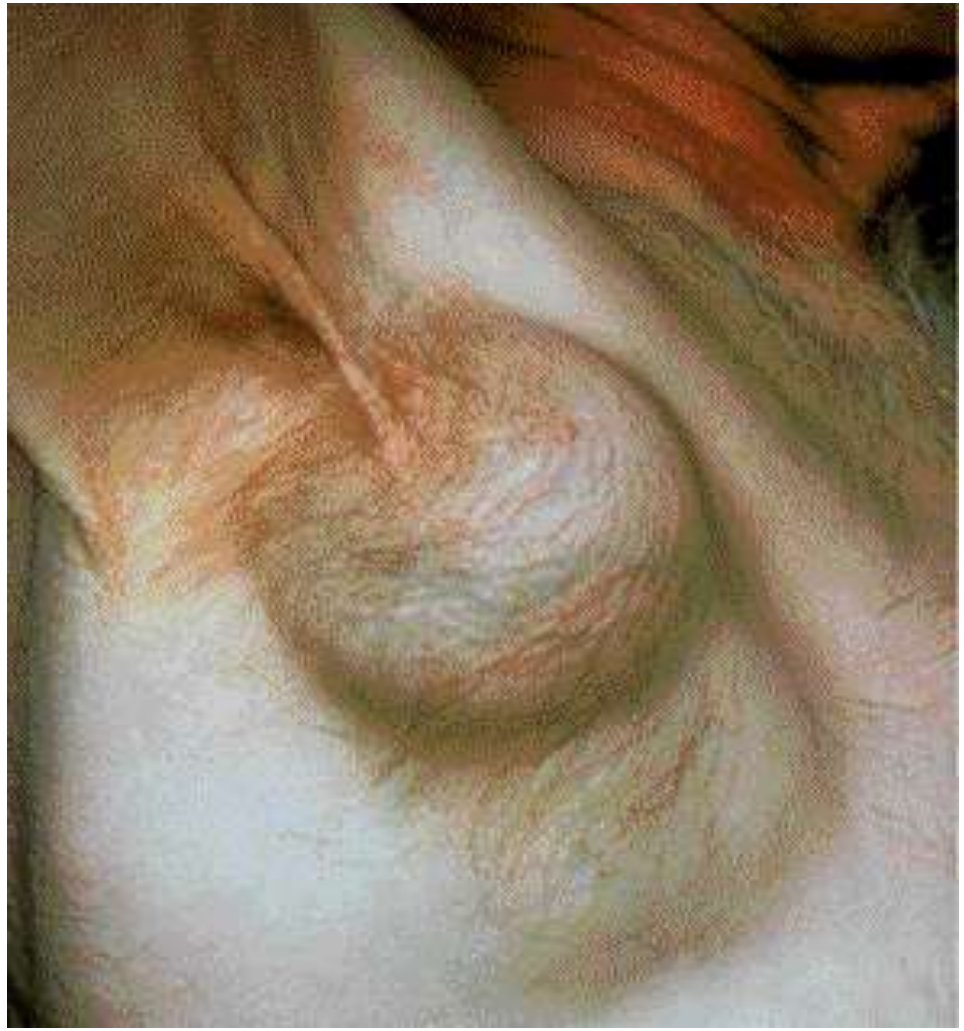
The progressive accumulation of leukemic B cells is a consequence of defective apoptosis and survival signals derived from the microenvironment.

Progressive disease results in dysregulation of the cellular and humoral components of the effector immune system, with a resultant increase in the incidence of infectious complications, which constitutes the leading cause of morbidity and mortality in this disease.

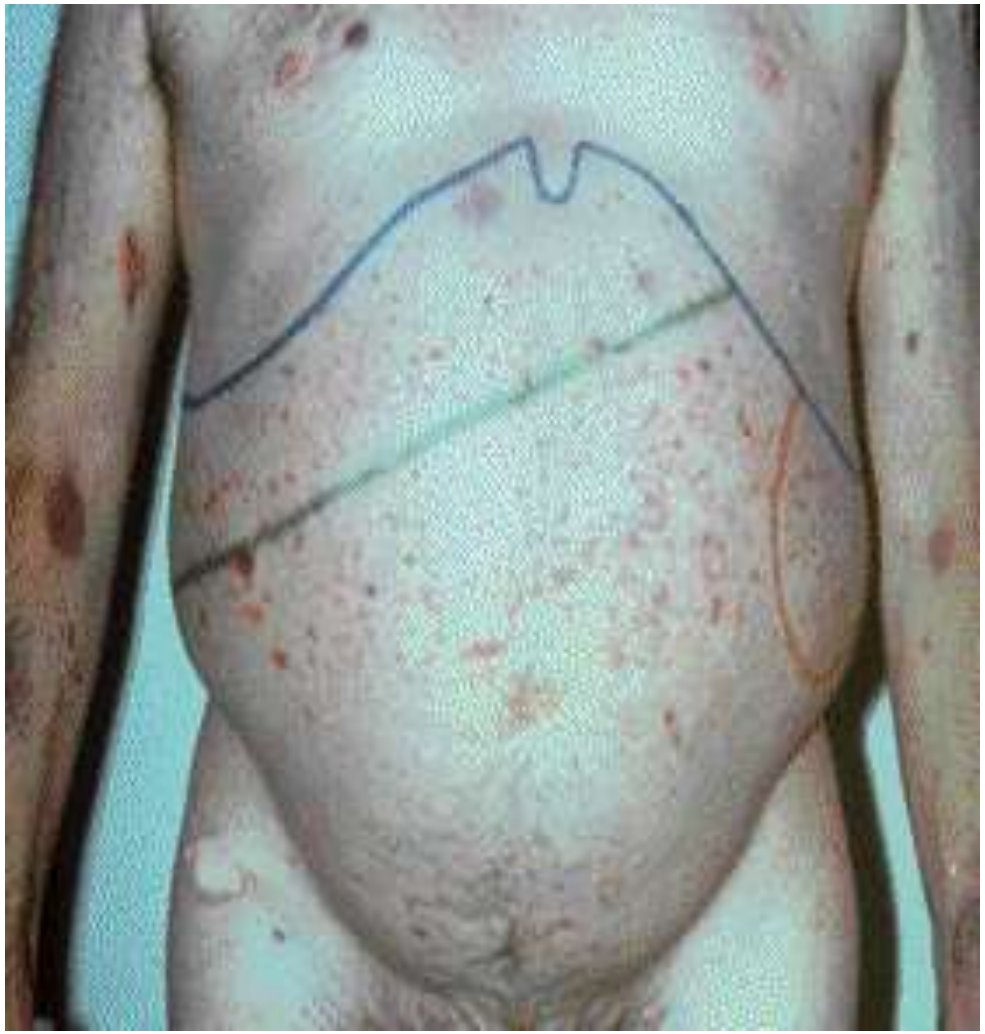
Clinical Features:

1. Asymptomatic.
2. LAP: Symmetrical enlargement of cervical, axillary, or inguinal LNs. It is usually discrete and non-tender.
3. Splenomegaly and less commonly hepatomegaly are common in the intermediate stage.
4. Features of anemia & thrombocytopenia are present in the advanced stage.
5. **Early** *bacterial* infections predominate but with **advanced** disease *viral and fungal* infections such as herpes zoster are also seen.

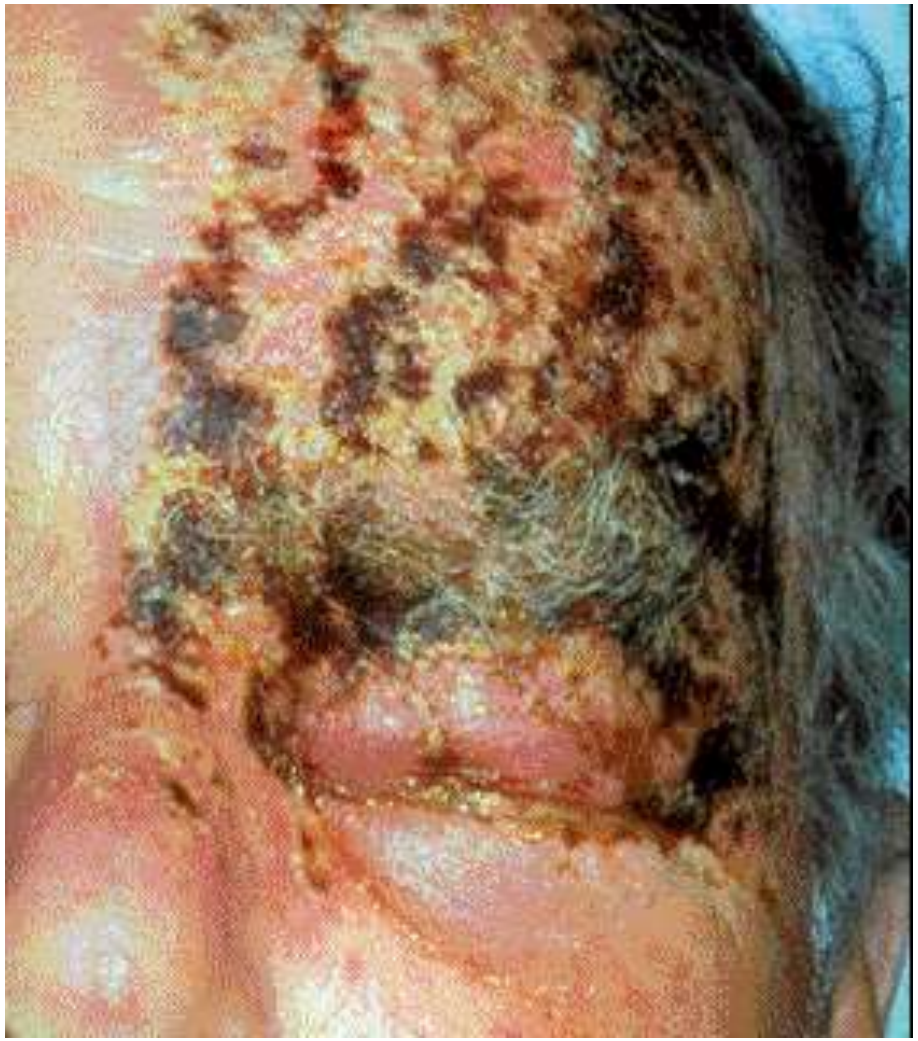
CLL; Axillary LAP



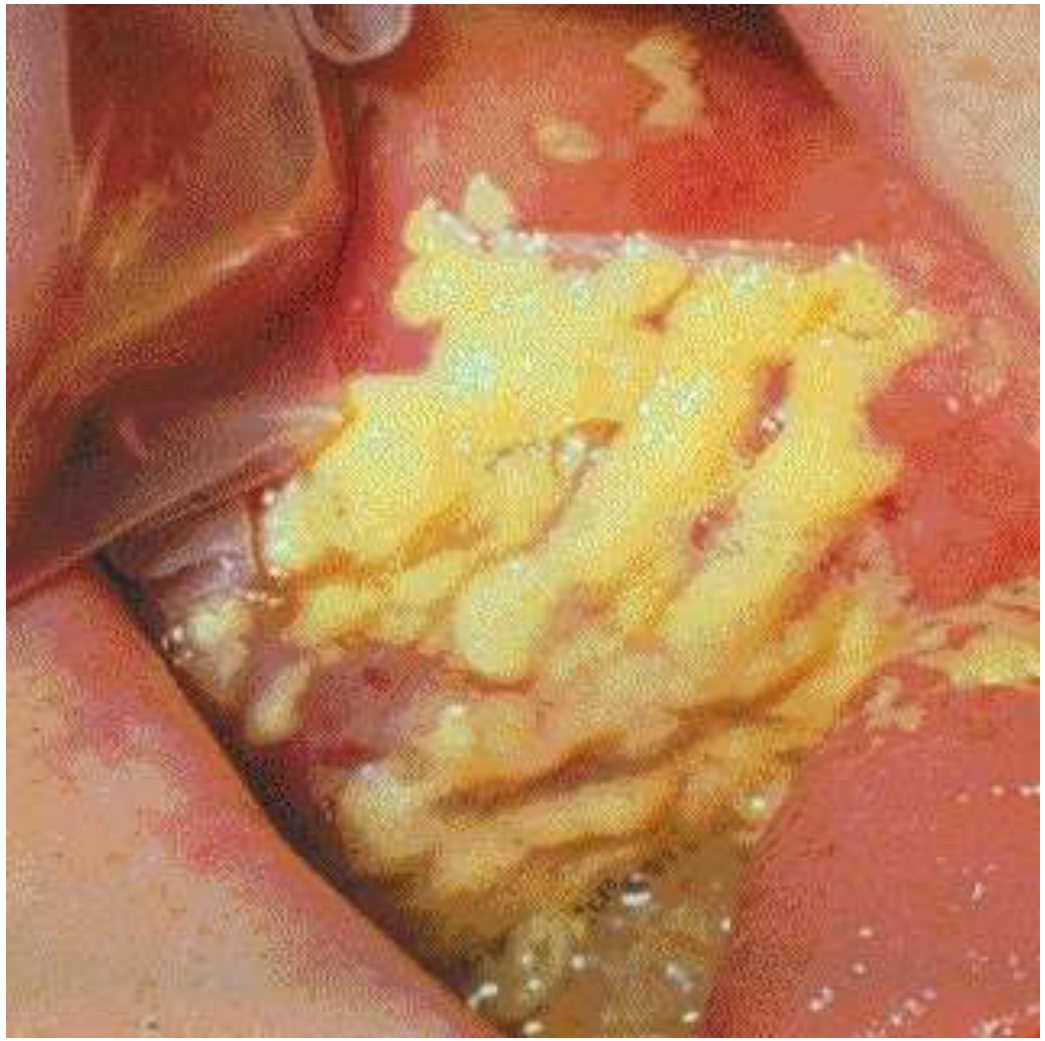
HSM with purpura & ecchymosis



CLL; Herpes zoster



Buccal Cavity: Candida albicans



Diagnosis of CLL:

There must be:

1. Sustained, persistent monoclonal B-cell lymphocytosis of $\geq 5 \times 10^9$/L in the PB with,

2. CLL immunophenotype (Score 4 or 5):
   - Pan-B-cell markers ($CD19^+$& $CD22^+$) with
   - Coexpression of $CD5^+$ & $CD23^+$ and
   - Weak expression of surface membrane immunoglobulin (SmIg for IgM or IgD) and
   - Weak or negative FMC7 and CD79b.

Immunophenotyping of CLL (CD19+ and CD22+)

Markers	CLL (score)
SmIg*	Weak (1)
CD5	+ (1)
CD23	+ (1)
FMC7♦	-/weak (1)
CD79b	-/weak (1)

*SmIg (surface membrane immunoglobulin for IgM or IgD)

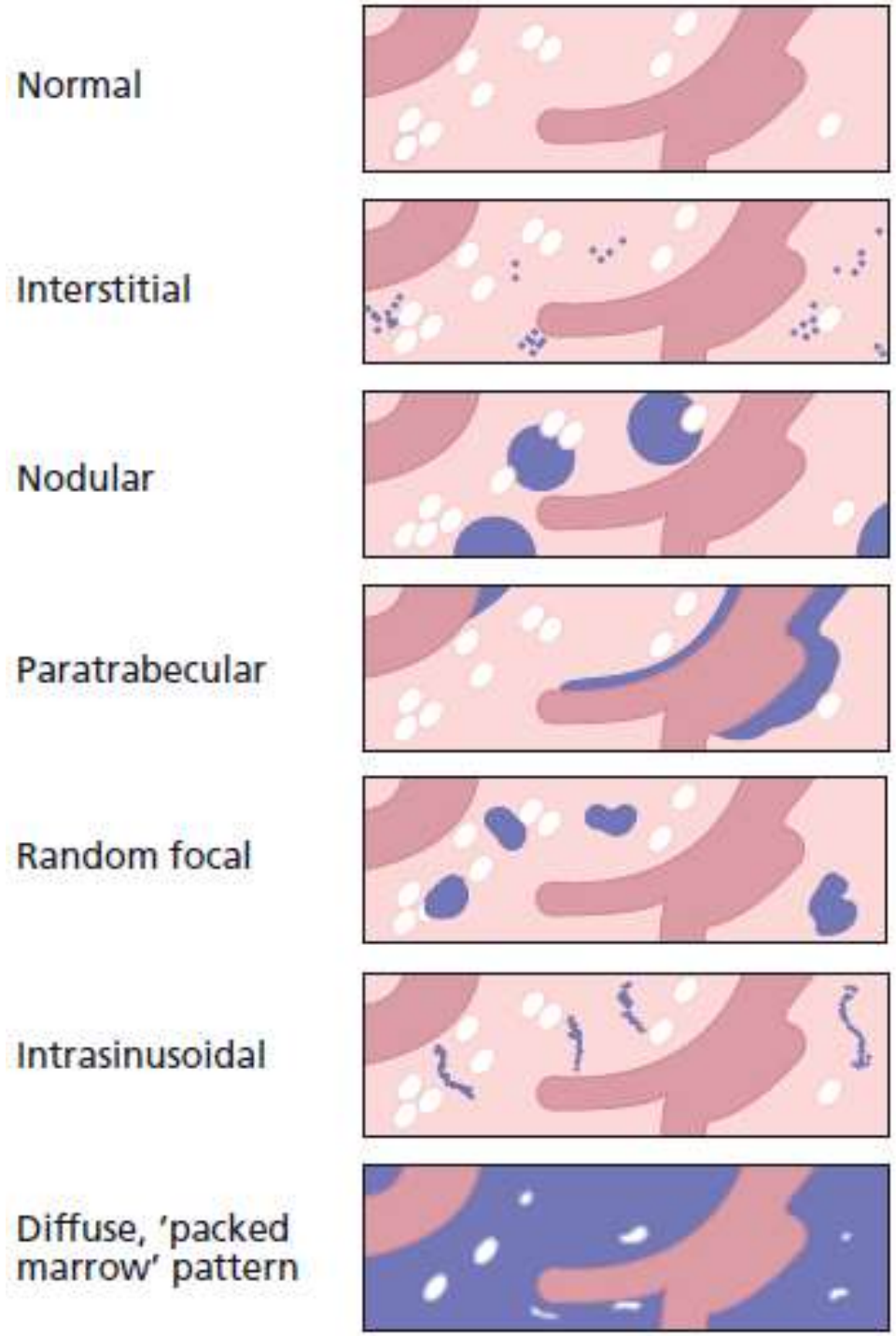
♦FMC7 is an epitope of CD20 but CD20 is not useful for scoring

Laboratory Findings:

1. Lymphocytosis: The predominant cells in the PB are small lymphocytes showing compact dark-staining round nuclei with scanty cytoplasm, and little variation in size with presence of the characteristic *smudge cells.*

2. Anemia and Thrombocytopenia are seen in later stages due to BM failure, or hypersplenism. AIHA and nutritional deficiencies may also occur.

3. BMA examination shows infiltration by lymphocytes.
   BM biopsy reveals early interstitial and late diffuse pattern of involvement.



Patterns of bone marrow infiltration observed in lymphoproliferative disorders

4. CLL Immunophenotype.

5. Serum Ig.

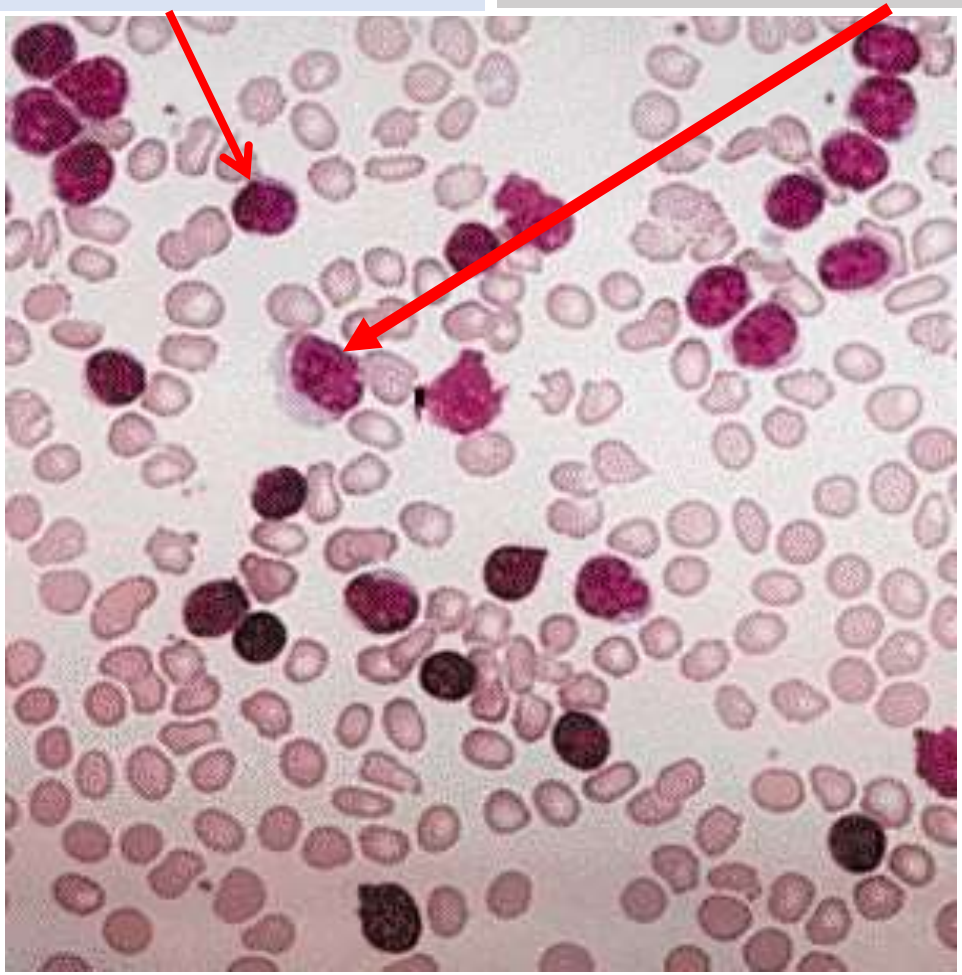
6. Karyotype. Most common cytogenetic abnormalities are:

- Deletion of 13q14 (good prognosis).
- Trisomy 12 associated with deletion at 11q23 and structural abnormalities of 17p involving the p53 gene (bad prognosis).

BF, CLL, showing mainly small mature-appearing lymphocytes with compact nuclear chromatin and scanty cytoplasm. Smudge cells and a large activated lymphocyte are also seen. The presence of jaundice, spherocytes and reticulocytosis with a positive direct Coombs test indicate the occurrence of autoimmune hemolytic anemia.

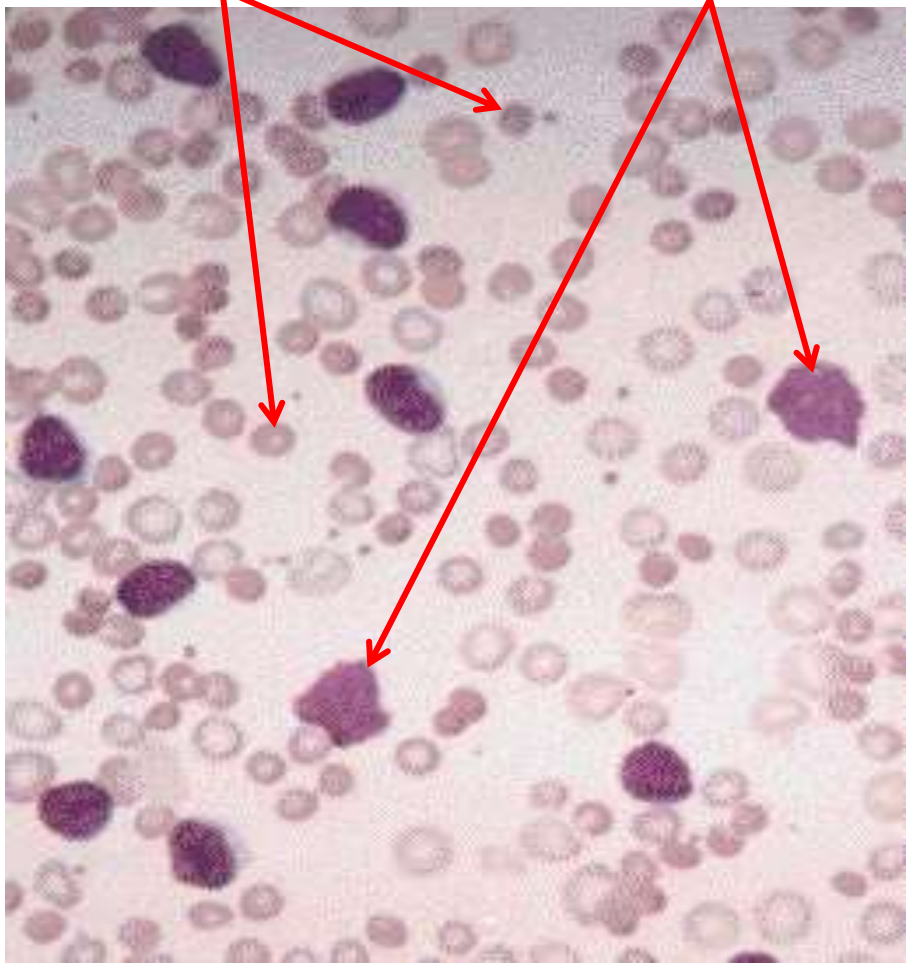
Leukemic lymphocytes

Large activated lymphocytes



Spherocytes in AIHA

Smudge cells



Staging of CLL:

It is useful to stage patients at presentation both for prognosis and for deciding on therapy

The stage is determined by several variables such as;

Peripheral lymphocytosis,

Presence or absence of LAP ± Hepatosplenomegaly.

The presence of anemia Hb <11g/dL and/or thrombocytopenia platelets <100 $\times 10^9$/L indicates advanced stage of the disease.

Secondary causes of anemia (e.g. nutritional deficiency) or AIHA or thrombocytopenia must be treated before staging

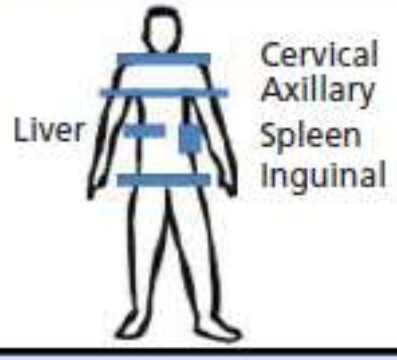
Clinical Staging of CLL

Rai	0	I	II	III	IV
Blood lymphocytosis	Yes	Yes	Yes	Yes	Yes
Lymphadenopathy	No	Yes	Yes/no	Yes/no	Yes/no
Spleen/liver enlargement	No	No	Yes	Yes/no	Yes/no
Hb <110 g/L	No	No	No	Yes	Yes/no
Platelets $<100\times10^9$/L	No	No	No	No	Yes
Median survival (years)	>15	7–9	6–8	3–5	3–5

Binet	A	B	C
Blood lymphocytosis	Yes	Yes	Yes
< 3 lymphoid areas* enlarged	No	Yes	Yes/no
Hb <110g/L and/or Platelets $<100\times10^9$ /L	No	No	Yes
Median survival (years)	>15	7–9	3–5

*cervical, axillary, inguinal lymph nodes (either uni- or bilateral), spleen, and liver.

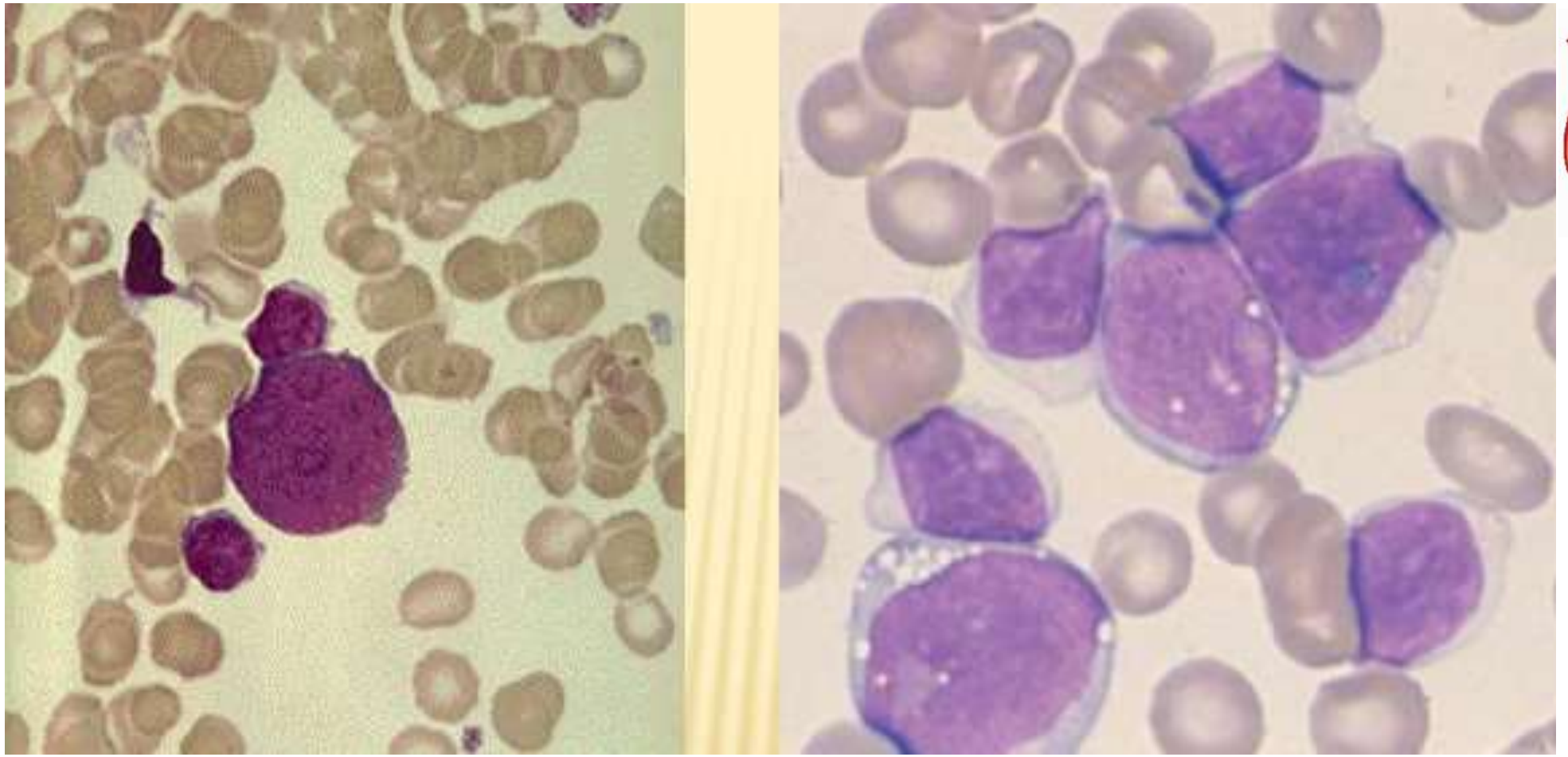
Binet 'lymphoid' areas



Course & Prognosis of CLL:

1. Survival ranges from 12 years for early stage to < 3 years for advanced stage.

2. CLL may transform to Richter's syndrome (Diffuse large B-cell lymphoma)



Blood film, Richter’s syndrome, showing circulating large blast cells that were positive for SmIg.

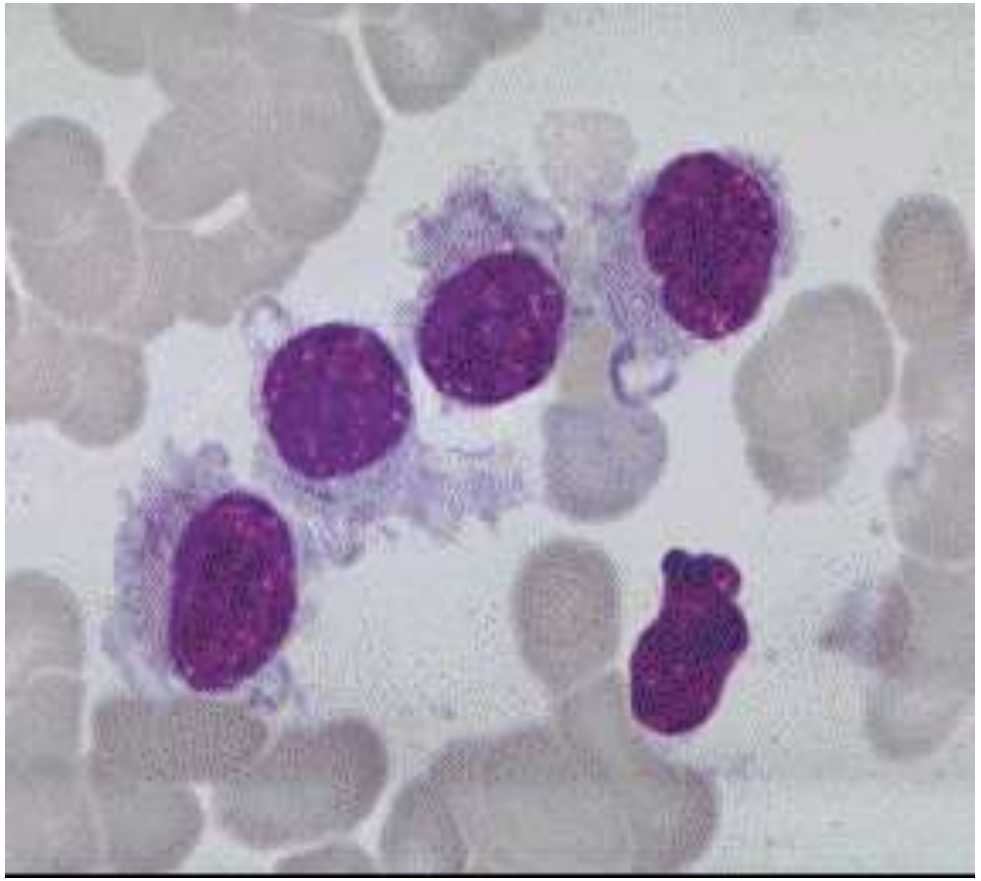
Hairy Cell Leukemia

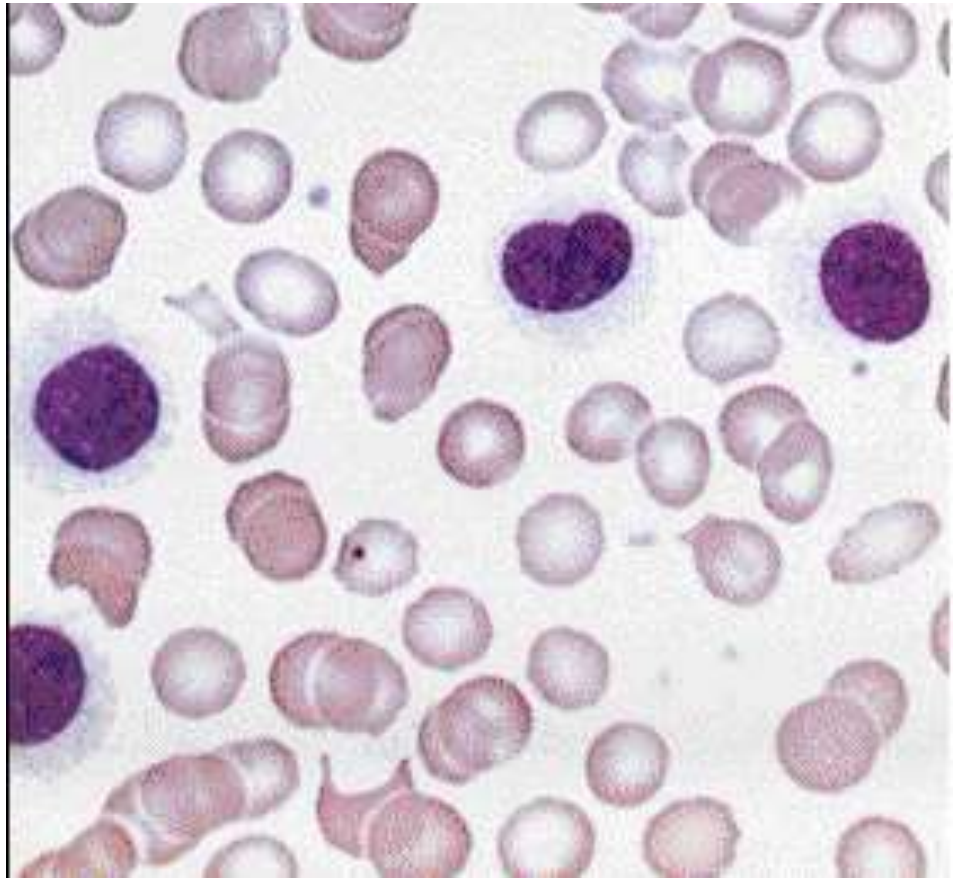
Clinically; infections, anemia, and splenomegaly. LAP is very uncommon.

Lab findings; *pancytopenia and monocytopenia*. Lymphocyte count is rarely > 20×10^9/L. The blood film reveals a variable number of unusually *large lymphocytes with villous cytoplasmic projections*.

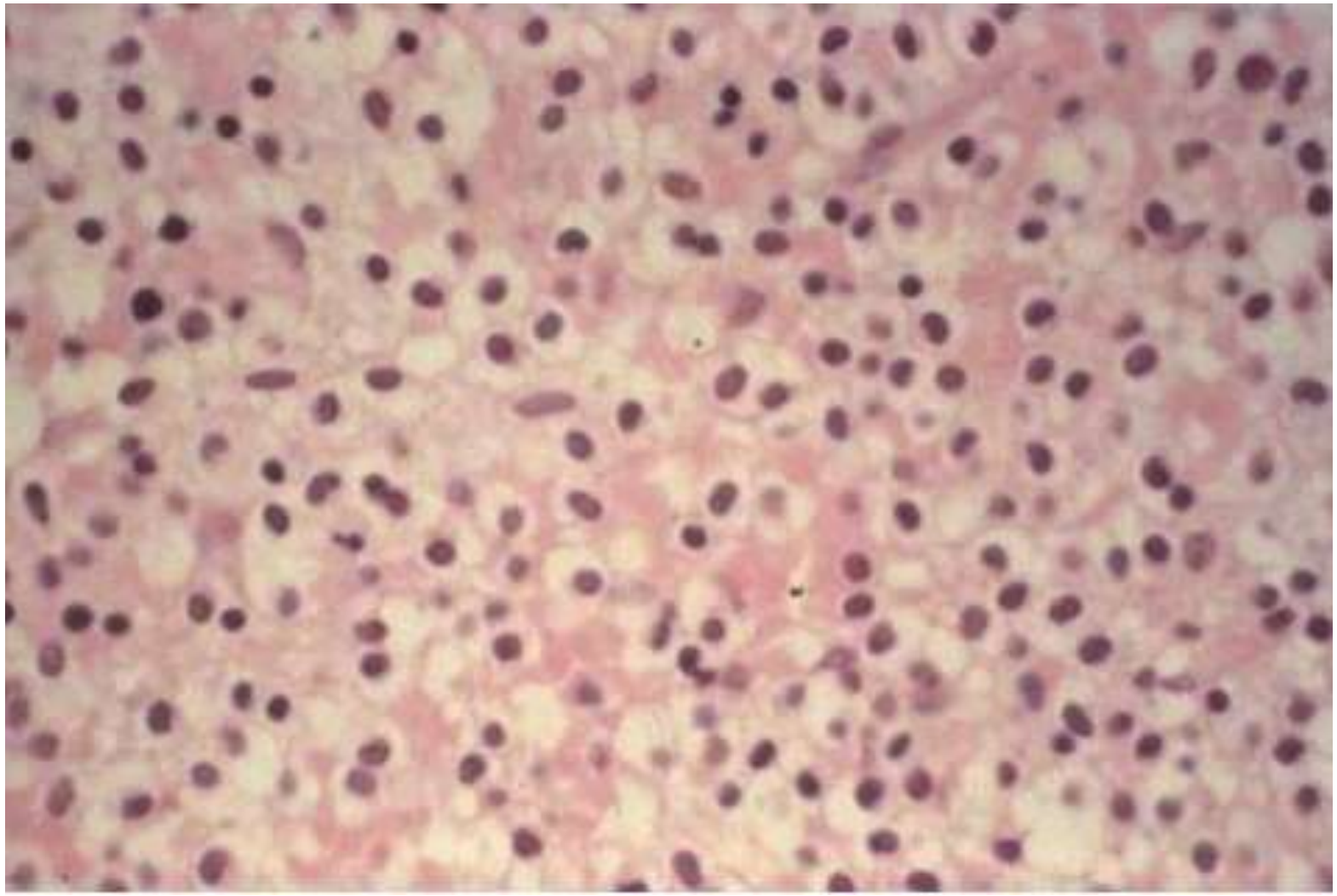
BM biopsy shows a characteristic appearance of mild fibrosis and a loose diffuse cellular infiltrate.

Patients can expect long-term remission with appropriate treatment.





BF, HCL, showing large lymphocytes with villous cytoplasmic projections



Bone marrow trephine section, HCL, showing the typical clear zone around the hairy cells in a paraffin-embedded section.

Presence of Bilateral symmetrical cervical and submandibular lymphadenopathy is consistent with which one of the following chronic LPDs?

A. Chronic lymphocytic leukemia.
B. Hairy cell leukemia.

A 54-year-old man presented with fever, and pallor for three-month duration. CBC revealed pancytopenia. On examination, there was splenomegaly with no lymphadenopathy. The blood film shows few large lymphocytes with villous cytoplasmic projections. The most likely diagnosis is:

A. Acute lymphoblastic leukemia.
B. Chronic myeloid leukemia.
C. Hairy cell leukemia.
D. Chronic lymphocytic leukemia.

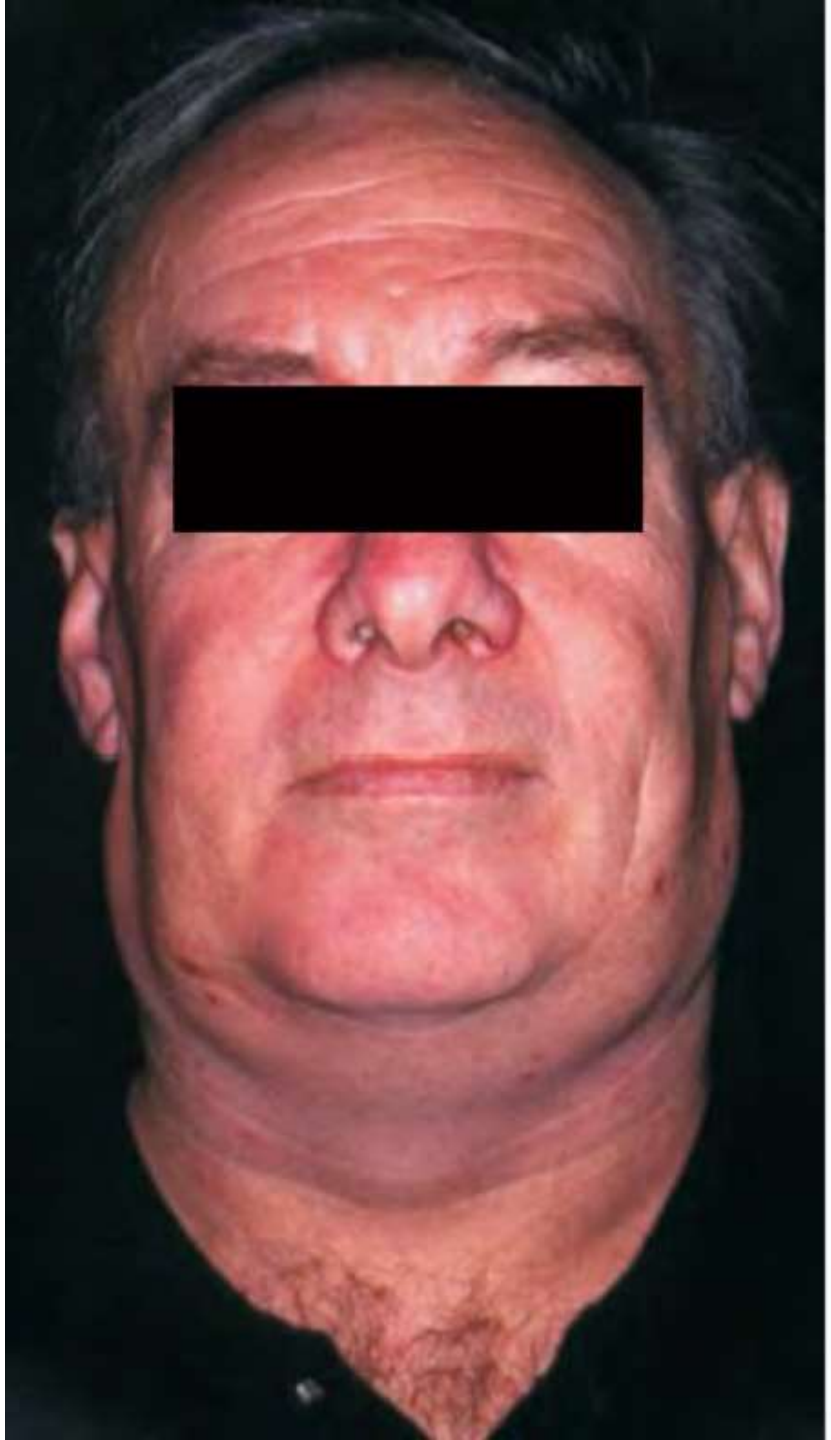
Case Scenario

A 62-year-old man who noticed a painless swelling in his neck over the last 2 weeks. There was NO family history of thyroid disease.

On physical exam, he had bilateral enlarged LNs in his Cervical, Submandibular and Supraclavicular regions (3 × 2 cm). They were non-tender, firm and fixed. The overlying skin appeared normal.

Axillary and inguinal LNs were also enlarged (3 × 3 cm)

The spleen was palpable 5 cm below the left lower costal margin.

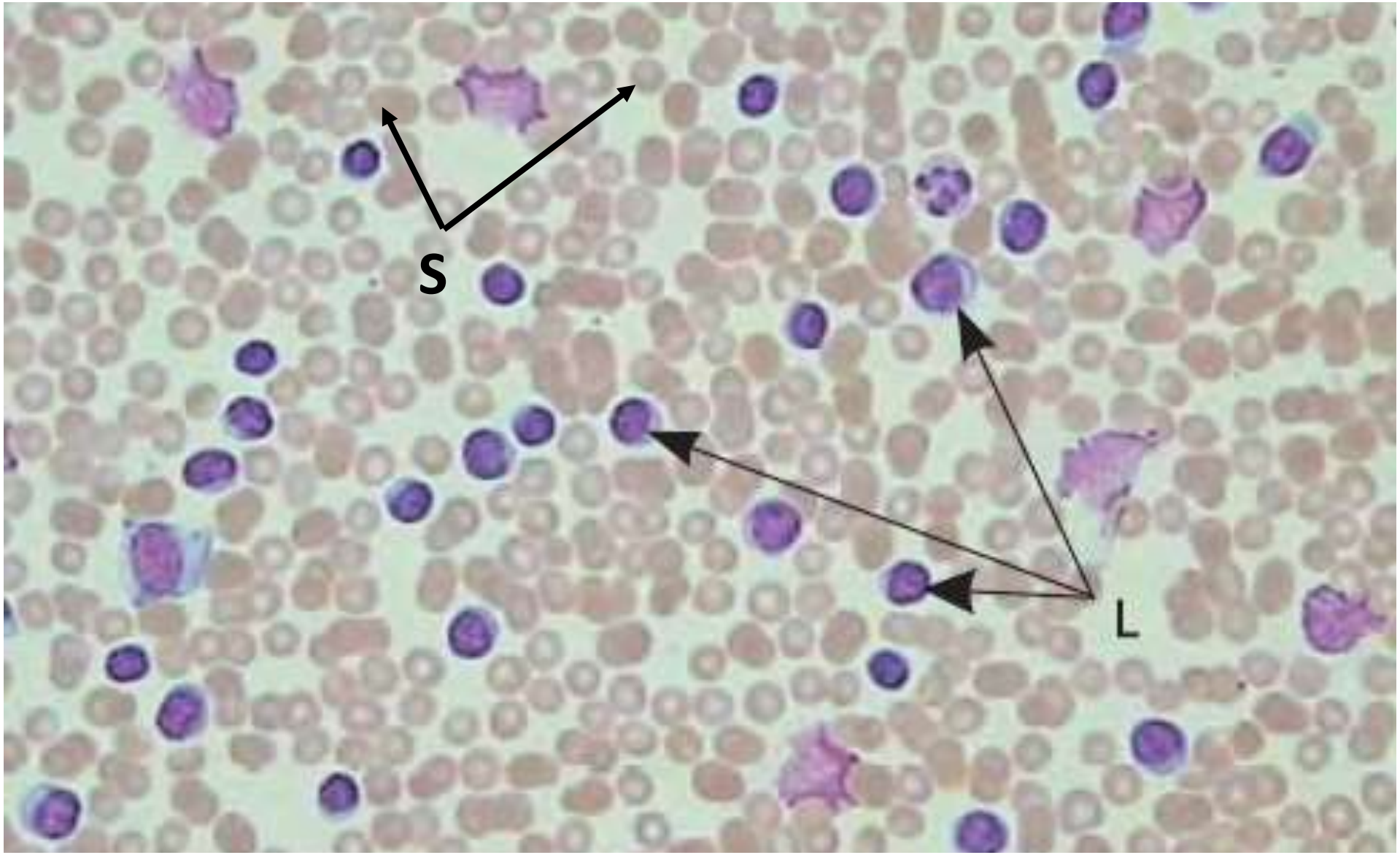


Enlarged lymph nodes in the neck

Full Blood Count:

		Patient's Results	Normal Range
Hb		13.9 g/dL	13.5 - 17.5 g/dL
WBC		55.0 × 10^9/L	4.0 - 11.0 × 10^9/L
Platelets		230 × 10^9/L	150 - 410 × 10^9/L
Neutrophils	10%	5.5 × 10^9/L	2.0 - 7.0 × 10^9/L
Lymphocytes	90%	49.5 × 10^9/L	1.5 - 3.5 × 10^9/L

►Blood Film: A predominance of lymphocytes in the blood (L) with many smudge cells (S).



What further investigations are required to confirm the diagnosis?

Flowcytometric Immunophenotyping study of:

- Pan-B-cell markers ($CD19^+$& $CD22^+$) with
- Co-expression of $CD5^+$ & $CD23^+$
- Weak expression of SmIg (for IgM or IgD)
- Weak or negative expression of FMC7 and
- Weak or negative expression of CD79b.

What is the diagnosis?

Chronic lymphocytic leukemia

Summary

- CLL is the most common among the LPDs.
- PB lymphocytosis ≥ 5 $\times 10^9$/L and CLL score of > 3 is sufficient for the diagnosis of CLL without the need of BM examination.
- LAP is uncommon in HCL and PLL.
- HCL may present with pancytopenia or leukocytosis (lymphocytosis) and appearing of the characteristic hairy cells in the PB.
- PLL presents with high absolute lymphocyte count.

End of WBC Part 2A