VASILE MUSTEATA, MD, PhD, MPH,
associate professor;
Discipline of Hematology,
State University of Medicine
and Pharmacy "N. Testemitanu"

HODGKIN LYMPHOMA
NON-HODGKIN LYMPHOMAS

CHISINAU – 2020

WHO CLASSIFICATION OF MYELOID NEOPLASMS AND ACUTE LEUKEMIA

(VARDIMAN et al., BLOOD, 30 JULY 2009 VOLUME 114, NUMBER 5)

MYELOPROLIFERATIVE NEOPLASMS (MPN)

- **Chronic myelogenous leukemia, *BCR-ABL1–positive***
- **Chronic neutrophilic leukemia**
- **Polycythemia vera**
- **Primary myelofibrosis**
- **Essential thrombocythemia**
- **Chronic eosinophilic leukemia, not otherwise specified**
- **Mastocytosis**
- **Myeloproliferative neoplasms, unclassifiable**

MYELOID AND LYMPHOID NEOPLASMS ASSOCIATED WITH EOSINOPHILIA AND ABNORMALITIES OF *PDGFRA, PDGFRB, OR FGFR1*

- **Myeloid and lymphoid neoplasms associated with *PDGFRA rearrangement***
- **Myeloid neoplasms associated with *PDGFRB rearrangement***
- **Myeloid and lymphoid neoplasms associated with *FGFR1 abnormalities***

MYELODYSPLASTIC/MYELOPROLIFERATIVE NEOPLASMS (MDS/MPN)

- **Chronic myelomonocytic leukemia**
- **Atypical chronic myeloid leukemia, *BCR-ABL1–negative***
- **Juvenile myelomonocytic leukemia**
- **Myelodysplastic/myeloproliferative neoplasm, unclassifiable**
  - ***Provisional entity: refractory anemia with ring sideroblasts and thrombocytosis***

WHO CLASSIFICATION OF MYELOID NEOPLASMS AND ACUTE LEUKEMIA

(VARDIMAN et al., BLOOD, 30 JULY 2009 VOLUME 114, NUMBER 5)

MYELODYSPLASTIC SYNDROME (MDS)

Refractory cytopenia with unilineage dysplasia

- **Refractory anemia**
- **Refractory neutropenia**
- **Refractory thrombocytopenia**

Refractory anemia with ring sideroblasts

Refractory cytopenia with multilineage dysplasia

Refractory anemia with excess blasts

Myelodysplastic syndrome with isolated del(5q)

Myelodysplastic syndrome, unclassifiable

Childhood myelodysplastic syndrome

- ***Provisional entity: refractory cytopenia of childhood***

ACUTE MYELOID LEUKEMIA AND RELATED NEOPLASMS

Acute myeloid leukemia with recurrent genetic abnormalities

- **AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1***
- **AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11***
- **APL with t(15;17)(q22;q12); *PML-RARA***
- **AML with t(9;11)(p22;q23); *MLLT3-MLL***
- **AML with t(6;9)(p23;q34); *DEK-NUP214***
- **AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1***
- **AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1***
  - ***Provisional entity: AML with mutated NPM1***
  - ***Provisional entity: AML with mutated CEBPA***

WHO CLASSIFICATION OF MYELOID NEOPLASMS AND ACUTE LEUKEMIA

(VARDIMAN et al., BLOOD, 30 JULY 2009 VOLUME 114, NUMBER 5)

Acute myeloid leukemia with myelodysplasia-related changes

Therapy-related myeloid neoplasms

Acute myeloid leukemia, not otherwise specified

- **AML with minimal differentiation**
- **AML without maturation**
- **AML with maturation**
- **Acute myelomonocytic leukemia**
- **Acute monoblastic/monocytic leukemia**
- **Acute erythroid leukemia**
  - **Pure erythroid leukemia**
  - **Erythroleukemia, erythroid/myeloid**

Acute megakaryoblastic leukemia

Acute basophilic leukemia

Acute panmyelosis with myelofibrosis

Myeloid sarcoma

Myeloid proliferations related to Down syndrome

- **Transient abnormal myelopoiesis**
- **Myeloid leukemia associated with Down syndrome**

Blastic plasmacytoid dendritic cell neoplasm

WHO CLASSIFICATION OF MYELOID NEOPLASMS AND ACUTE LEUKEMIA

(VARDIMAN et al., BLOOD, 30 JULY 2009 VOLUME 114, NUMBER 5)

ACUTE LEUKEMIAS OF AMBIGUOUS LINEAGE

Acute undifferentiated leukemia

Mixed phenotype acute leukemia with t(9;22)(q34;q11.2); *BCR-ABL1*

Mixed phenotype acute leukemia with t(v;11q23); *MLL rearranged*

Mixed phenotype acute leukemia, B-myeloid, NOS

Mixed phenotype acute leukemia, T-myeloid, NOS

Provisional entity: natural killer (NK) cell lymphoblastic leukemia/lymphoma

B LYMPHOBLASTIC LEUKEMIA/LYMPHOMA

B lymphoblastic leukemia/lymphoma, NOS

B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities

- **B lymphoblastic leukemia/lymphoma with t(9;22)(q34;q11.2); *BCR-ABL 1***
- **B lymphoblastic leukemia/lymphoma with t(v;11q23); *MLL rearranged***
- **B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22) *TEL-AML1* (*ETV6-RUNX1)***
- **B lymphoblastic leukemia/lymphoma with hyperdiploidy**
- **B lymphoblastic leukemia/lymphoma with hypodiploidy**
- **B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32) *IL3-IGH***
- **B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *TCF3-PBX1***

T LYMPHOBLASTIC LEUKEMIA/LYMPHOMA

WHO CLASSIFICATION OF TUMOURS OF HAEMATOPOIETIC AND LYMPHOID TISSUES

(Swerdlow S.H., Campo E, Harris NL et al, eds. Lyon: IARC Press, 2008)

MATURE B-CELL NEOPLASMS

Chronic lymphocytic leukemia/small lymphocytic lymphoma

B-cell prolymphocytic leukemia

Splenic B-cell marginal zone lymphoma

Hairy cell leukemia

Splenic lymphoma/leukemia, unclassifiable (provisional)

- **Splenic diffuse red pulp small B-cell lymphoma (provisional)**
- **Hairy cell leukemia-variant (provisional)**

Lymphoplasmacytic lymphoma

- **Waldenström macroglobulinemia**

Heavy chain diseases

- **α Heavy chain disease**
- **γ Heavy chain disease**
- **μ Heavy chain disease**

Plasma cell myeloma

Solitary plasmacytoma of bone

Extraosseous plasmacytoma

Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)

Nodal marginal zone lymphoma

- **Pediatric nodal marginal zone lymphoma (provisional)**

Follicular lymphoma

- **Pediatric follicular lymphoma (provisional)**

WHO CLASSIFICATION OF TUMOURS OF HAEMATOPOIETIC AND LYMPHOID TISSUES

(Swerdlow S.H., Campo E, Harris NL et al, eds. Lyon: IARC Press, 2008)

Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma (DLBCL), not otherwise specified
- **T-cell/histiocyte-rich large B-cell lymphoma**
- **Primary DLBCL of the CNS**
- **Primary cutaneous DLBCL, leg type**
- **EBV-positive DLBCL of the elderly (provisional)**

DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK-positive DLBCL
Plasmablastic lymphoma
Large B-cell lymphoma arising in HHV8-associated multicentric
- **Castleman disease**

Primary effusion lymphoma
Burkitt lymphoma
B-cell lymphoma, unclassifiable, with features intermediate between
- **diffuse large B-cell lymphoma and Burkitt lymphoma**

B-cell lymphoma, unclassifiable, with features intermediate between
- **diffuse large B-cell lymphoma and classic Hodgkin lymphoma**

WHO CLASSIFICATION OF TUMOURS OF HAEMATOPOIETIC AND LYMPHOID TISSUES

(Swerdlow S.H., Campo E, Harris NL et al, eds. Lyon: IARC Press, 2008)

MATURE T-CELL AND NK CELL NEOPLASMS

T-cell prolymphocytic leukemia

T-cell large granular lymphocytic leukemia

Chronic lymphoproliferative disorder of NK cells (provisional)

Aggressive NK cell leukemia

Systemic EBV-positive T-cell lymphoproliferative disease of childhood

Hydroa vacciniforme-like lymphoma

Adult T-cell leukemia/lymphoma

Extranodal NK/T-cell lymphoma, nasal type

Enteropathy-associated T-cell lymphoma

Hepatosplenic T-cell lymphoma

Subcutaneous panniculitis-like T-cell lymphoma

Mycosis fungoides

Sézary syndrome

Primary cutaneous CD30+ T-cell lymphoproliferative disorders

- **Lymphomatoid papulosis**
- **Primary cutaneous anaplastic large cell lymphoma**

Primary cutaneous *g/d T-cell lymphoma*

Primary cutaneous CD8+ aggressive epidermotropic cytotoxic T-cell lymphoma (provisional)

Primary cutaneous CD4+ small/medium T-cell lymphoma (provisional)

Peripheral T-cell lymphoma, not otherwise specified

Angio-immunoblastic T-cell lymphoma

Anaplastic large cell lymphoma, ALK positive

Anaplastic large cell lymphoma, ALK negative (provisional)

WHO CLASSIFICATION OF TUMOURS OF HAEMATOPOIETIC AND LYMPHOID TISSUES

(Swerdlow S.H., Campo E, Harris NL et al, eds. Lyon: IARC Press, 2008)

HODGKIN LYMPHOMA

Nodular lymphocyte-predominant Hodgkin lymphoma

Classic Hodgkin lymphoma

- **Nodular sclerosis classic Hodgkin lymphoma**
- **Lymphocyte-rich classic Hodgkin lymphoma**
- **Mixed cellularity classic Hodgkin lymphoma**
- **Lymphocyte-depleted classic Hodgkin lymphoma**

HISTIOCYTIC AND DENDRITIC CELL NEOPLASMS

Histiocytic sarcoma

Langerhans cell histiocytosis

Langerhans cell sarcoma

Interdigitating dendritic cell sarcoma

Follicular dendritic cell sarcoma

Fibroblastic reticular cell tumor

Indeterminate dendritic cell tumor

Disseminated juvenile xanthogranuloma

POST-TRANSPLANT LYMPHOPROLIFERATIVE DISORDERS (PTLD)

Early lesions

- **Plasmacytic hyperplasia**
- **Infectious mononucleosis-like PTLD**

Polymorphic PTLD

Monomorphic PTLD (B- and T/NK cell types)

Classic Hodgkin lymphoma type PTLD

B-CELL DEVELOPMENT AND THE CORRESPONDING LYMPHOMAS DERIVED AT EACH STAGE

(American Society of Hematology, New Approaches to Lymphoma Diagnosis. Hematology 2001)

	B-Cells	Immunoglobulin Genes	Somatic Mutations	Ig Protein	Marker	Corresponding Lymphoma	
Foreign antigen	Stem cell	Germ line	None	None	CD34		Bone marrow
independent	Pro-B-cell [§]	Germ line	None	None	CD19, CD79a, BSAP, CD34, CD10, TdT		
	Pre-B-cell *	IgH rearrangement μ-chain (Cytoplasm)	None	Igμ	CD19, CD45R, CD79a, BSAP, CD34, CD10, TdT	**B-LBL/ALL**	
	Immature B-Cell	IgL/IgH-rearrangements IgM (Membrano)	None	IgM (Membrane)	CD19, CD20, CD45R, CD79a, CD10 BSAP		
Foreign antigen dependent	Mature naive B-cell	IgH/L rearrangements IgM und IgD (Membrane)	None	IgM/IgD	CD19, CD20, CD45R, CD79a, BSAP, CD5	**B-CLL, MCL**	**Peripheral lymphoid tissue**
	Germinal Center (CB and CC)	IgH/L rearrangements Class switch	Introduction of somatic mutations	Ig (minimal or absent)	CD19, CD20, CD45R, CD79a, BSAP, CD10, BCL6	**BL, FL, LPHL, DLBCL, cHL[§]**	
	Memory B-Cell	IgH/L rearrangements	Somatic mutations	IgM	CD19, CD20, CD45R, CD79a, BSAP	**MZL, B-CLL**	
Terminal Differentiation	Plasma cell	IgH/L rearrangements	Somatic mutations	IgG>IgA> IgD	CD38, Vs38c, MUM-1, CD138	**Plasmacytoma/ myeloma**	

[§] There is a developmental stage between the Pro-B-cell and the Pre-B-cell for which no universally accepted term exists. Terms previously used are: "pre-pre-B" or "common B-cell precursor." This intermediate cellular stage most commonly gives rise to B-LBL/ALL.

* For a detailed description of the Ig-gene rearrangement events early and late pre-B-cells are distinguished (see Table 2).

[§] The relationship to germinal center cells can only be determined by molecular biological investigations, as the phenotype of the tumor cells is completely changed following the malignant transformation.

Abbreviations: CB, centroblasts; CC, centrocytes; Ig, Immunoglobulin; B-LBL, B-cell lymphoblastic lymphoma; B-CLL, chronic lymphocytic leukemia; MCL, mantle cell lymphoma; BL, Burkitt lymphoma; FL, follicle center lymphoma; LPHL, lymphocyte-predominant Hodgkin lymphoma; DLBCL, diffuse large cell B-cell lymphoma; cHL, classic Hodgkin lymphoma; MZL, marginal zone B-cell lymphoma.

HODGKIN LYMPHOMA

HODGKIN LYMPHOMA (HL) **is a clinicopathologically aggressive B-cell lymphoma, which is one of the most curable of all haematological malignancies. The annual incidence of HL ranges between 1.47 – 2.8 cases per 100.000 population. This malignancy occurs mostly in population with the age of 5 – 9, 40 – 49, 60 – 69 years old in males and 20 – 29, 60 – 69 years old in females. Male : female ratio may reach 1.4-1.5 : 1.**

The demonstration of clonal rearrangements of the immunoglobulin heavy- and light-chain loci has confirmed their B-cell origin. The presence of somatic hypermutation within the immunoglobulin heavy and light chain loci suggest that HRS cells are derived from B-lymphocytes with germinal centre exposure. Despite their B-cell ontogenesis, HRS cells have lost most of the normal B-cell lineage gene expression program (including the expression of immunoglobulin) through numerous aberrant genetic mechanisms, such as epigenetic silencing at B-cell gene promoter regions.

Source: Postgraduate Haematology, Seventh Edition. Edited by A Victor Hoffbrand, Douglas R Higgs, David M Keeling and Atul B Mehta. © 2016 JohnWiley & Sons, Ltd. Published 2016 by JohnWiley & Sons, Ltd.

HODGKIN LYMPHOMA

MOLECULAR PATHOGENESIS. **Genes involved in normal B-lymphocyte growth and differentiation are suppressed in HRS cells. Instead, numerous aberrant intracellular signalling pathways contribute to the malignant phenotype of HRS cells including the following:**

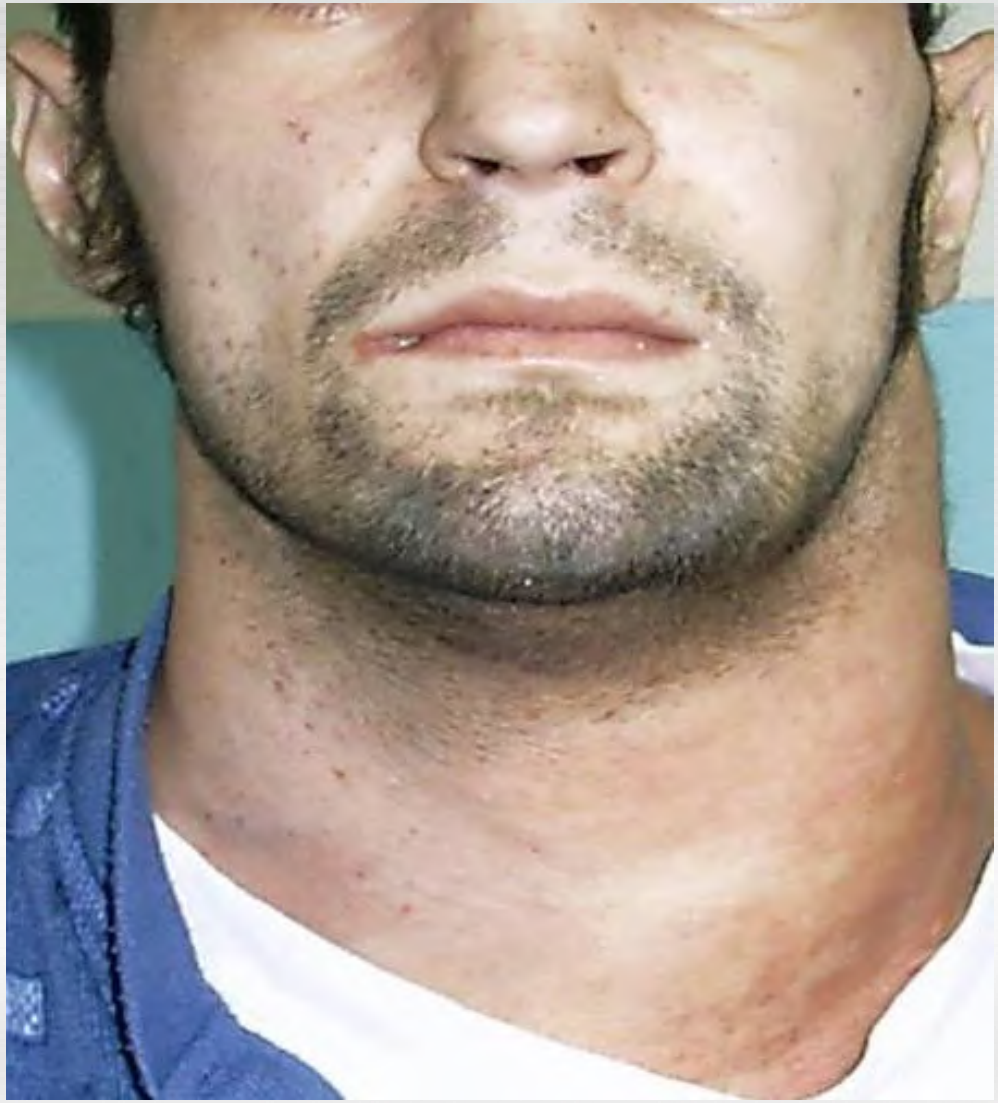
HRS cells show constitutive activation of the NF-κB pathway, which is associated with apoptosis resistance. The basis for constitutive NF-κB activation in at least a proportion of cases is the result of inactivating mutations in *TNFAIP3 and NFKBIA,* which encode inhibitors of the NF-κB pathway.

The JAK-STAT signalling pathway is overactive in HRS cells, resulting in uncontrolled growth and proliferation. Mechanisms of JAK-STAT over-activity include chromosomal gains at 9p24.1-24.3 (which includes the JAK2 locus) and inactivating mutations in *PTPN1 (leading to increased phosphorylation of* JAK-STAT pathway members).

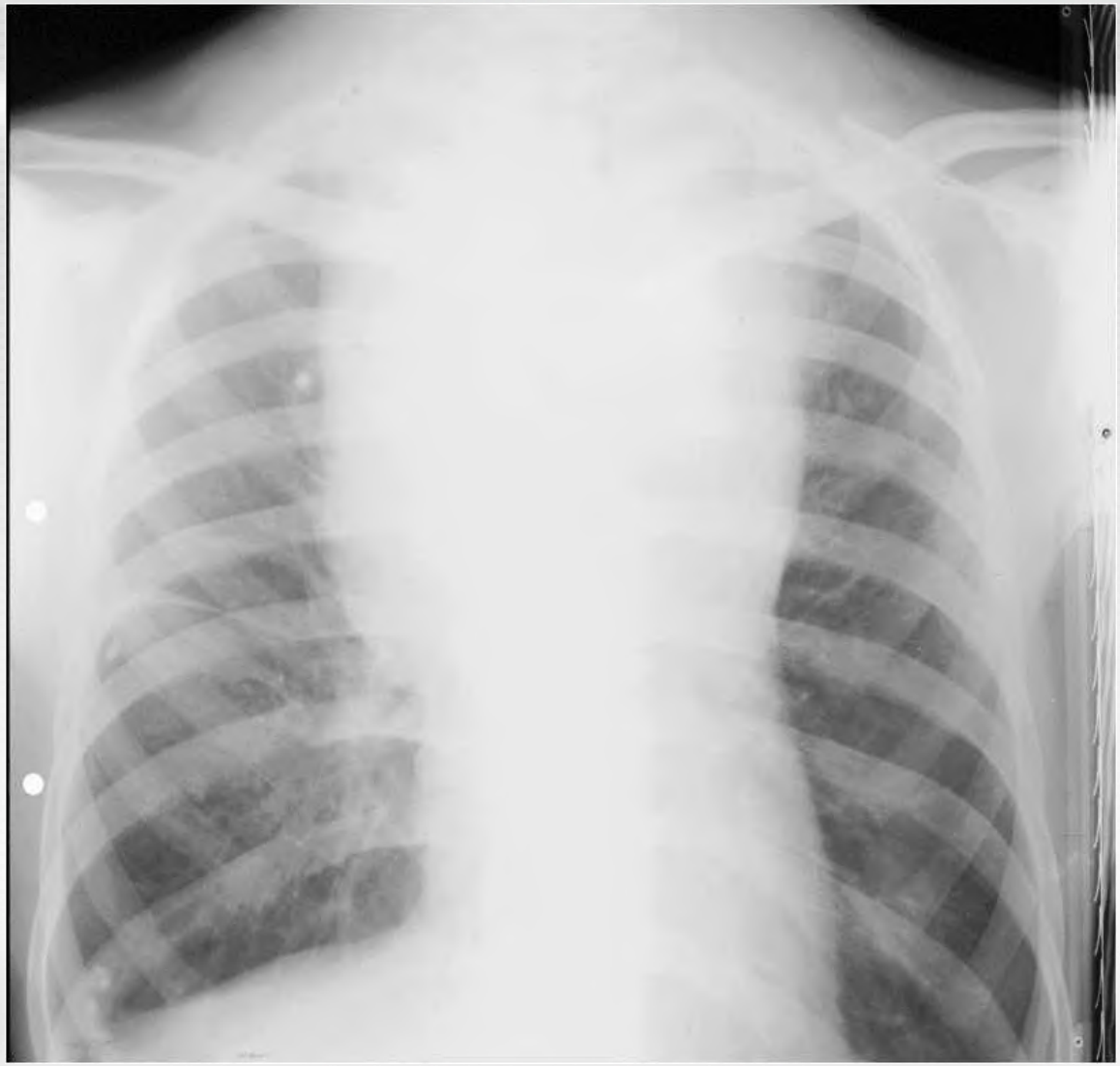
HRS cells have been shown to have deacetylated histones (H3), increased H3K27 trimethylation and DNA methylation patterns, leading to silencing of tumour-suppressor genes and the extinction of the normal B-lymphocyte expression profile.

High-throughput sequencing studies have detected deleterious mutations in β2M which could potentially contribute to immune evasion by HRS cells through decreased β2M expression.

CLINICAL EXAMINATION OF PATIENT WITH HODGKIN LYMPHOMA: CERVICAL LYMPH NODE ENLARGEMENT

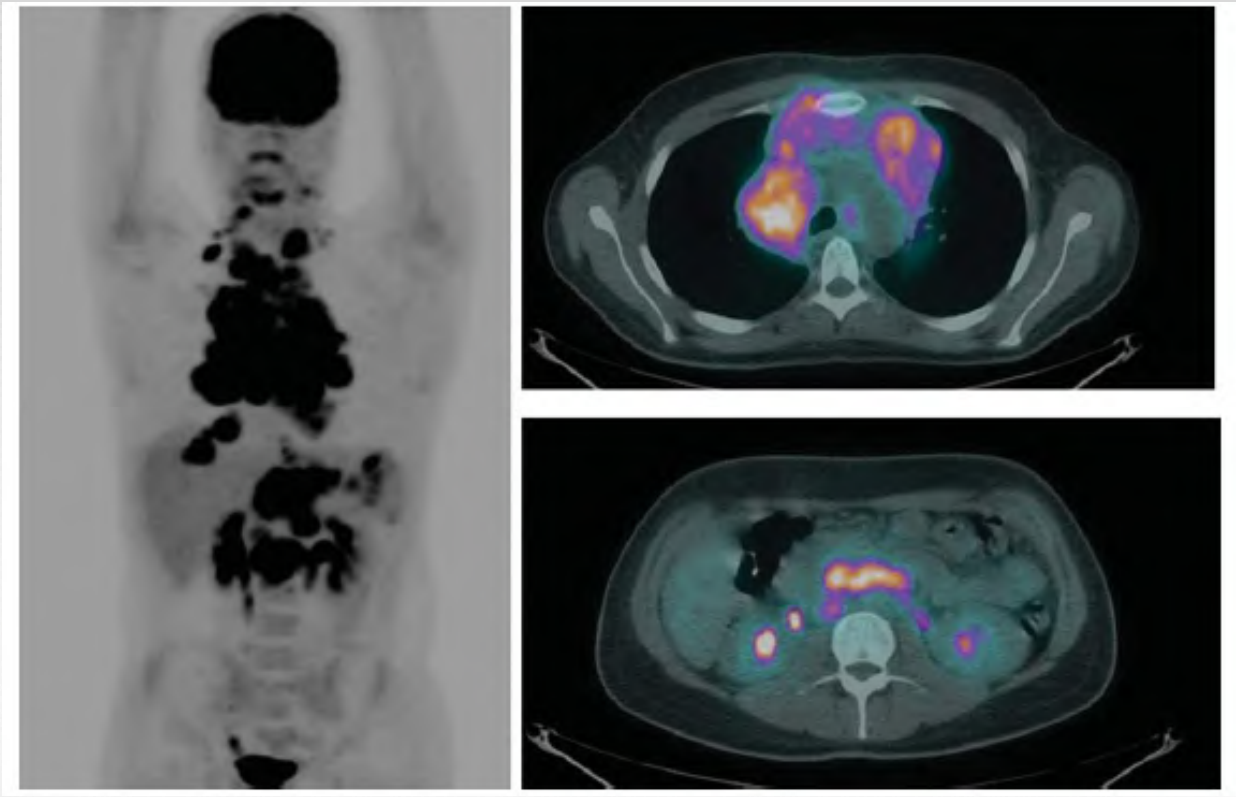


X-RAY EXAMINATION IN HODGKIN LYMPHOMA



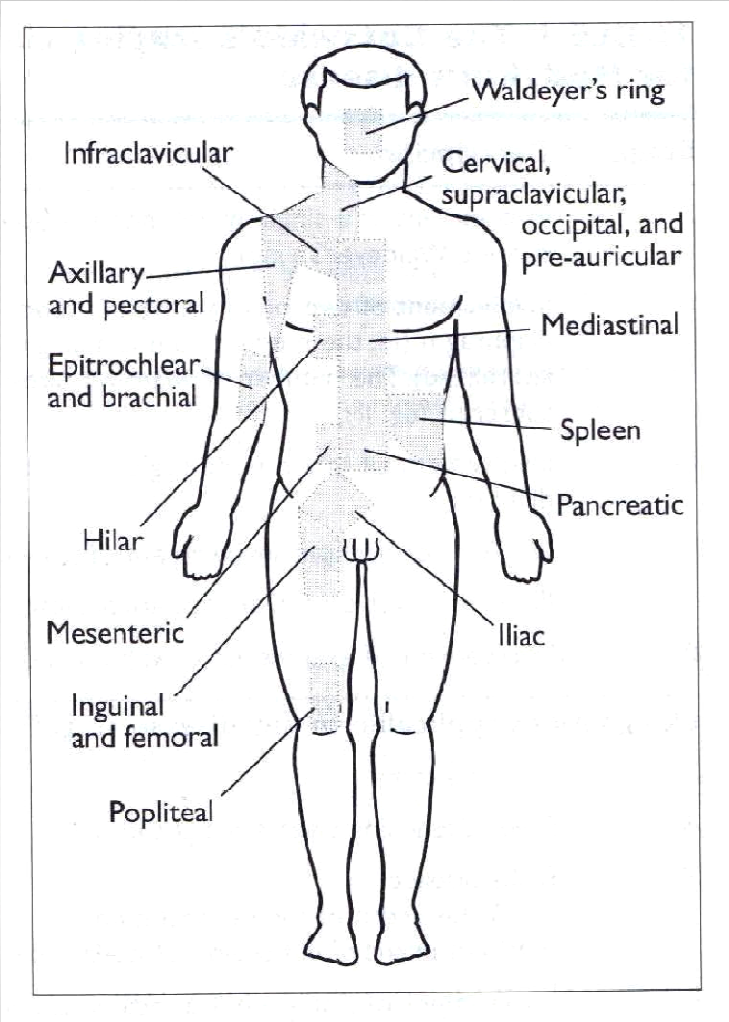
Thorax survey demonstrates mediastinal lymph node enlargement

PET scan images of patient with stage III HL showing FDG-avid cervical, mediastinal, mesenteric and retroperitoneal lymphadenopathy



ANATOMIC REGIONS FOR STAGING OF HODGKIN LYMPHOMA

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)



STAGING CLASSIFICATION OF HODGKIN LYMPHOMA:

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)

Stage	Description
I	Involvement of a single lymph node region or lymphoid structure (eg, spleen, thymus, Waldeyer's ring)
II	Involvement of two or more lymph node regions on the same side of the diaphragm (ie, the mediastinum is a single site, hilar lymph nodes are lateralized). The number of anatomic sites should be indicated by a subscript (eg, II_2).
III	Involvement of lymph node regions or structures on both sides of the diaphragm:
	III_1: With or without involvement of splenic, hilar, celiac, or portal nodes
	III_2: With involvement of para-aortic, iliac, or mesenteric nodes
IV	Involvement of extranodal site(s) beyond that designated E
Designations applicable to any disease stage[a]	
A	No symptoms
B	Fever, drenching sweats, weight loss
X	Bulky disease: > 1/3 the width of the mediastinum > 10 cm maximal dimension of nodal mass
E	Involvement of a single extranodal site, contiguous or proximal to a known nodal site
CS	Clinical stage
PS	Pathologic stage

[a] For examples of how these designations are applied to disease stage, see text discussion.

Elevated levels of fibrinogen (>5.0 g/l), α_2-globulin (>10 g/l), erythrocyte sedimentation rate (> 30mm/h), haptoglobin (>1.5mg%) are considered the signs of biological activity of Hodgkin lymphoma (if present, designation *b* is used).

PROGNOSTIC SCORING STAGING SYSTEM FOR HODGKIN LYMPHOMA:

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)

EARLY STAGES

Favorable	CS I and II (maximum 3 involved areas) and < 50 years *and* ESR < 50 mm/h (no B symptoms) *or* ESR < 30 mm/h (B symptoms present) *and* MT ratio < 0.35
Unfavorable	CS II ≥ 4 nodal areas involved *or* age ≥ 50 years *or* ESR ≥ 50 mm/h (no B symptoms) *or* ESR ≥ 30 mm/h (B symptoms present) *or* MT ratio ≥ 0.35

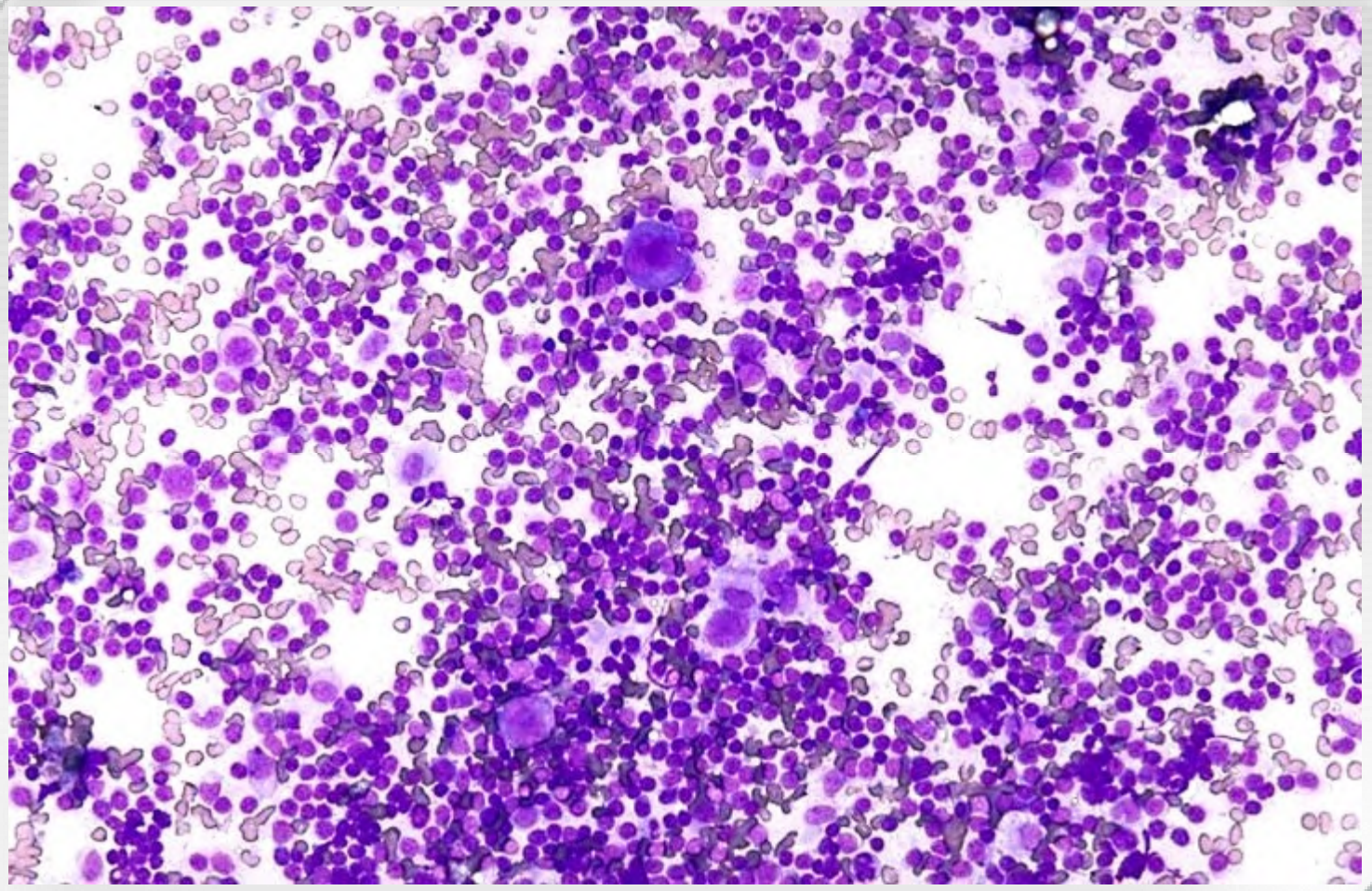
CS = Cotswald's staging; EORTC = European Organization for Research and Treatment of Cancer
ESR = erythrocyte sedimentation rate; MT = mediastinal/thoracic

ADVANCED STAGES

Serum albumin <4 g/dL
Hemoglobin <10.5 g/dL
Male sex
Stage IV disease
Age ≥45 years
White cell count >15,000/μL
Lymphocyte count <600/μL or <8% of total white cell count

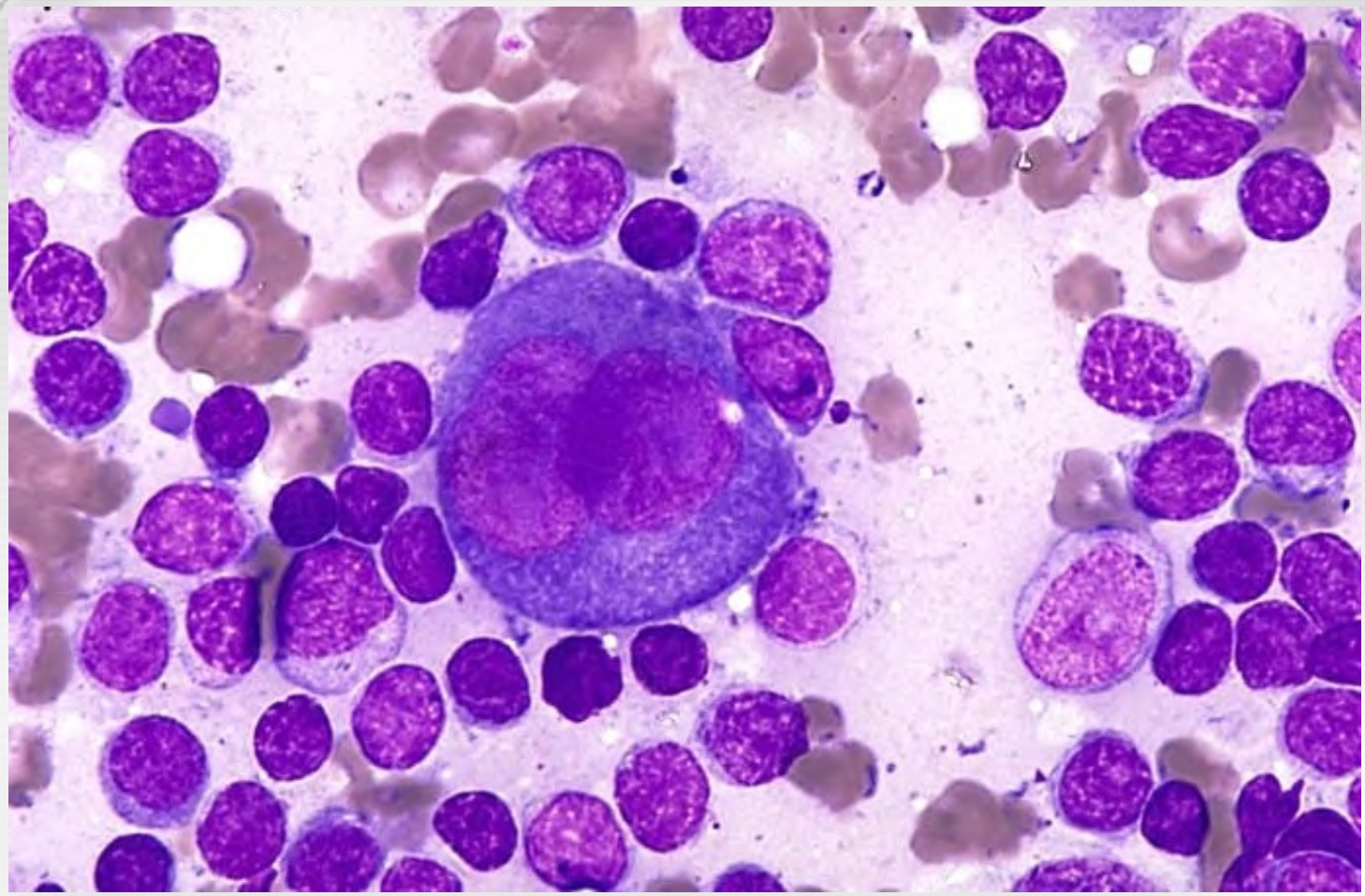
*From Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin disease. N Engl J Med. 1998;339:1506.

HODGKIN LYMPHOMA



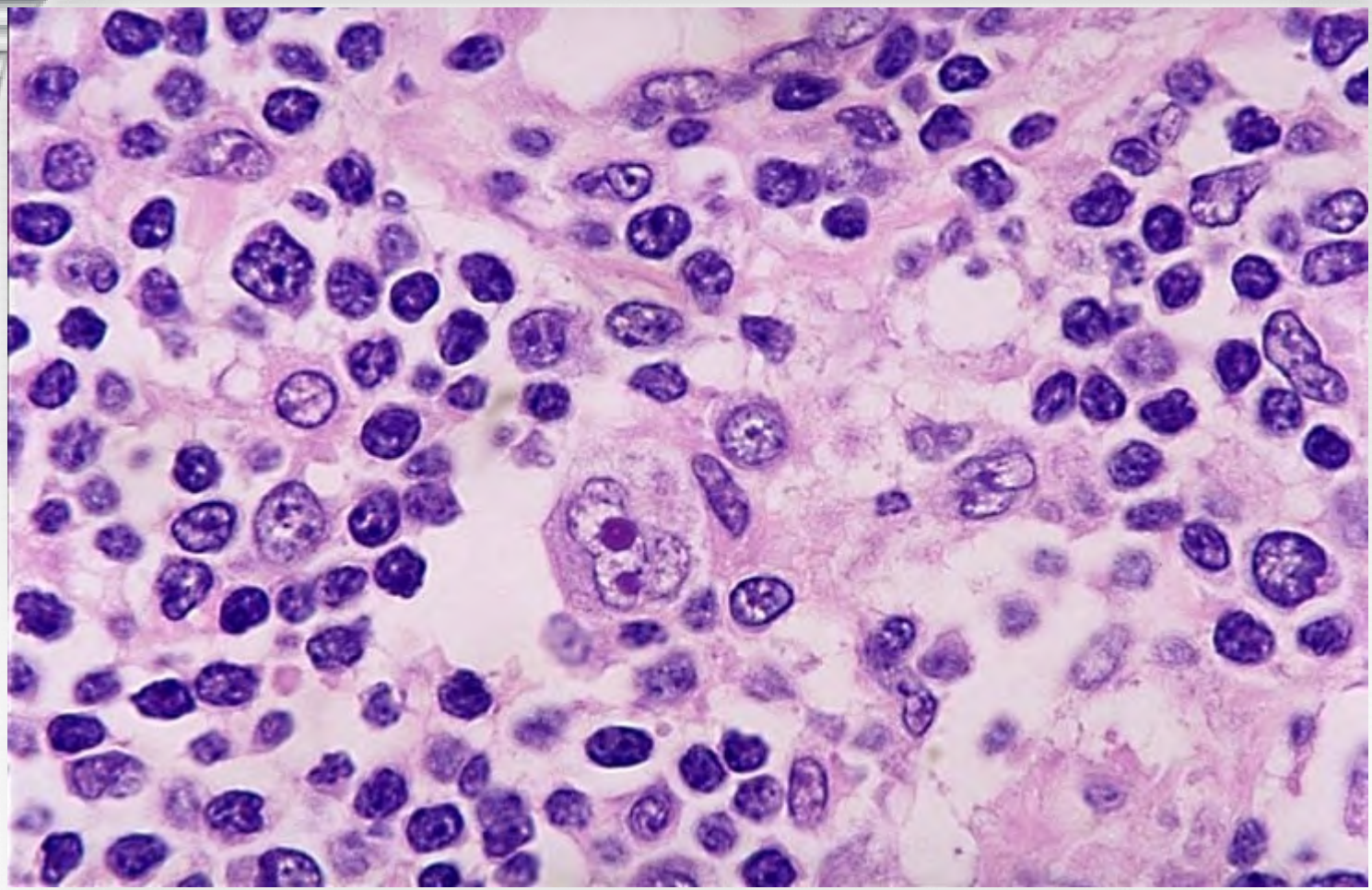
Touch preparation: binucleated large R-S cells.
May-Giemsa staining, x 200.

HODGKIN LYMPHOMA



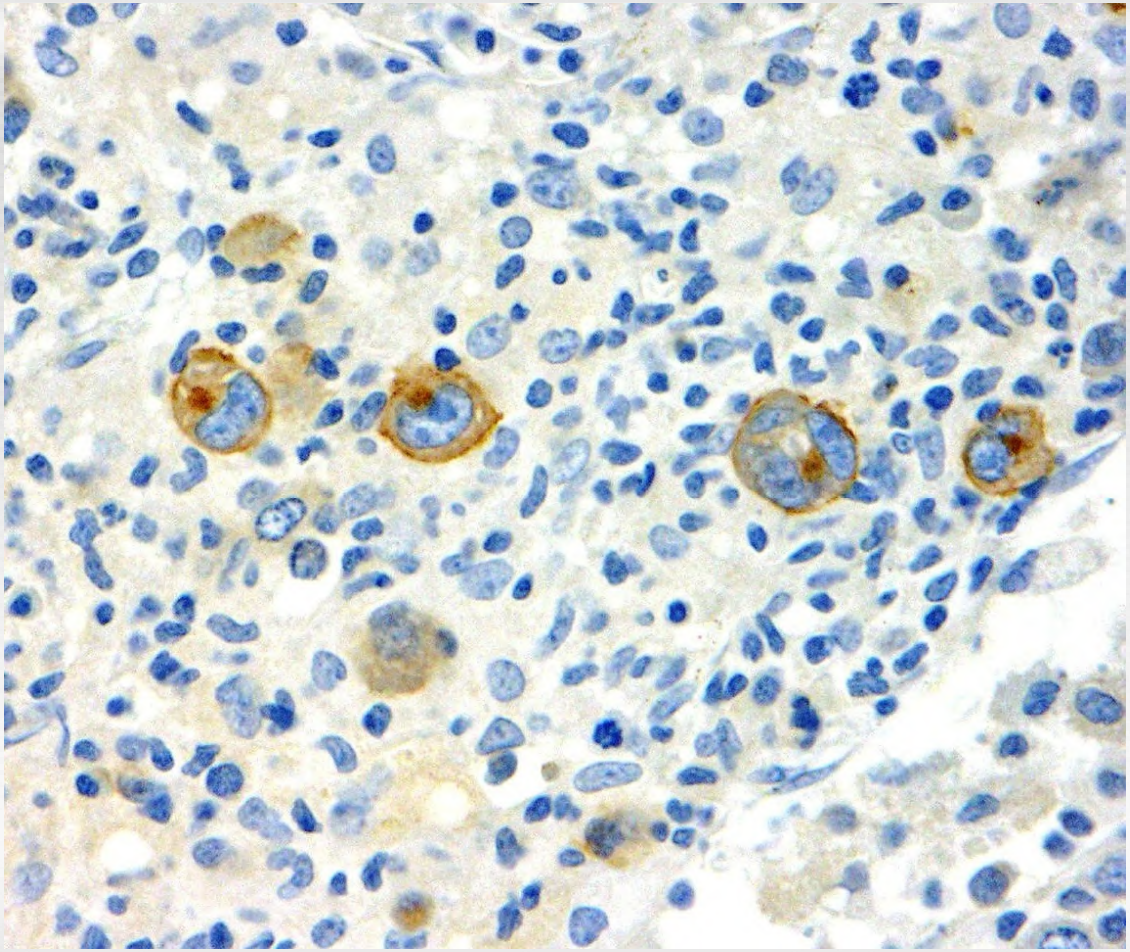
Touch preparation: binucleated large R-S cells.
May-Giemsa staining, x 1000.

HODGKIN LYMPHOMA



Lymph node.
Hematoxylin and eosin stain, x1000

HODGKIN LYMPHOMA



Immune phenotyping: large R-S cells positive for CD30.
May-Giemsa staining, x 1000.

FIRST-LINE CHEMOTHERAPY REGIMENS FOR HODGKIN LYMPHOMA

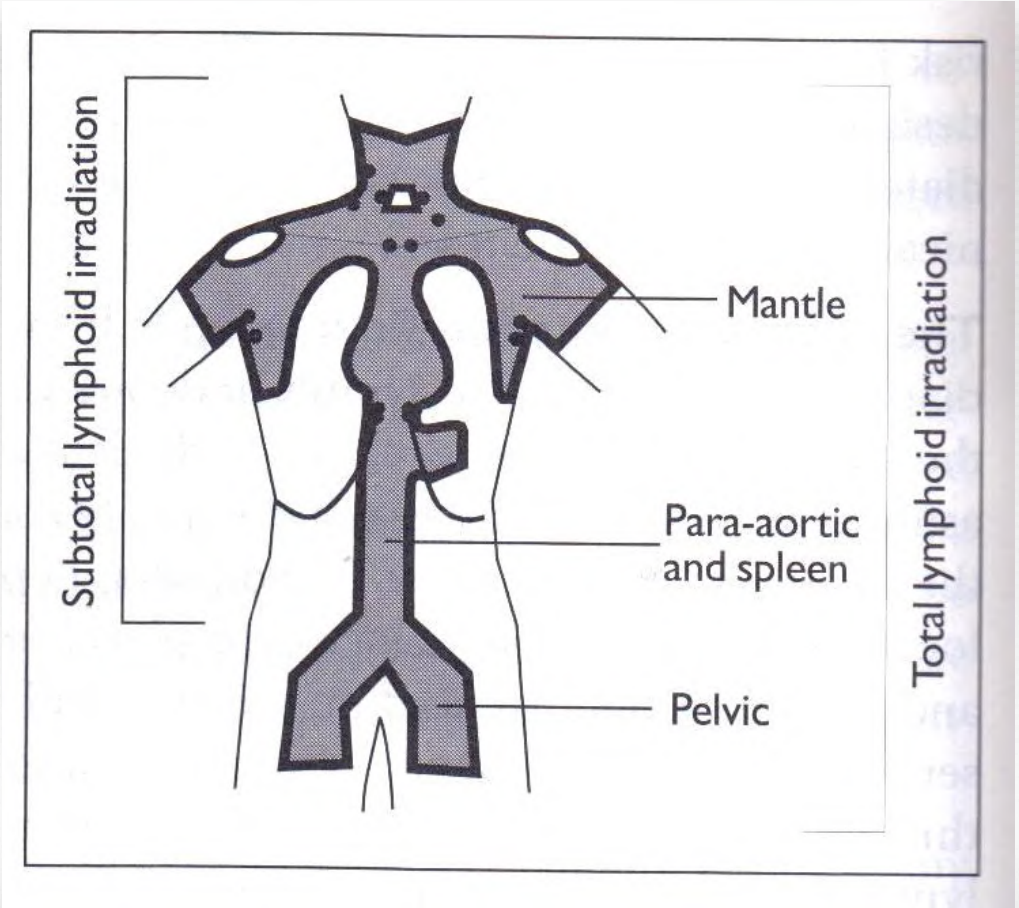
(Byrne B.J., Gockerman J.P. The Oncologist 2007;12:156–167)

Regimen/reference	Chemotherapy
ABVD [15]	25 mg/m^2 doxorubicin; days 1, 15
	10 U/m^2 bleomycin; days 1, 15
	6 mg/m^2 vinblastine; days 1, 15
	375 mg/m^2 dacarbazine; days 1, 15
BEACOPP [13]	650 mg/m^2 cyclophosphamide; day 1
	25 mg/m^2 doxorubicin; day 1
	100 mg/m^2 etoposide; days 1–3
	100 mg/m^2 procarbazine; days 1–7
	40 mg/m^2 prednisone; days 1–14
	1.4 mg/m^2 vincristine (2-mg maximum); day 8
	10 U/m^2 bleomycin; day 8
Escalated BEACOPP [13]	1200 mg/m^2 cyclophosphamide; day 1
	35 mg/m^2 doxorubicin; day 1
	200 mg/m^2 etoposide; days 1–3
	100 mg/m^2 procarbazine; days 1–7
	40 mg/m^2 prednisone; days 1–14
	1.4 mg/m^2 vincristine (2-mg maximum); day 8
	10 U/m^2 bleomycin; day 8
	G-CSF from day 8
MOPP [16]	6 mg/m^2 mechlorethamine; days 1, 8
	1.4 mg/m^2 vincristine; days 1, 8
	100 mg/m^2 procarbazine daily; days 1–14
	40 mg/m^2 prednisone; days 1–14
Stanford V [10]	**Weeks 1, 3, 5, 7, 9, and 11**
	25 mg/m^2 doxorubicin
	6 mg/m^2 vinblastine
	6 mg/m^2 mechlorethamine; weeks 1, 5, and 9 only
	Weeks 2, 4, 6, 8, 10, and 12
	1.4 mg/m^2 vincristine (2-mg maximum)
	5 U/m^2 bleomycin
	Weeks 3, 7, and 11 for 2 consecutive days
	60 mg/m^2 etoposide
	Weeks 1–12
	40 mg/m^2 prednisone every other day for 10 weeks and then tapered by 10 mg every other day; followed by consolidative irradiation

Abbreviation: G-CSF, granulocyte cell-stimulating factor.

EXTENDED RADIATION FIELDS USED FOR TREATMENT OF CLASSIC HODGKIN LYMPHOMA

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)



NON-HODGKIN'S LYMPHOMAS

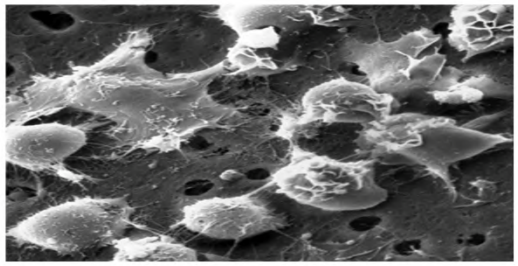
NON-HODGKIN'S LYMPHOMAS (HL) **are a heterogenous group of neoplastic disorders originating from the extramedullary hematopoietic lymphoid cells.**

The incidence of NHL in Republic of Moldova constitutes 4.1 per 100 000 population. Age–adjusted incidence rate are somewhat higher in males (4.7) than in females (3.6). Age–specific incidence rates show a logarithmic rise with increasing age. The mean age at diagnosis is 45 to 55 years. Considerable geographic and racial variations in overall incidence as well as histologic and immunologic subtypes are found worldwide, with a lower incidence of follicular lymphomas in China and Japan.

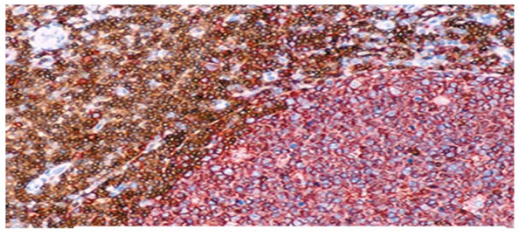
Pathogenesis. **The heterogenity of NHL suggests that a variety of factors including genetic abnormalities, immune disturbances, infectious agents, and other events interact in their pathogenesis. While morphology correlates with immunologic cell type (immunophenotyping), cells of identical appearance may be of types as disparate as T and B cells. Each of histologic types of NHL has its own prototype of normal cell, which NHL develop from after malignant transformation.**

The development of NHL is unifocal. The morphological composition of tumour determines the clinical course of NHL. Under certain conditions, low-grade histologic types can turn into high-grade histologic types and nodular forms of tumour gowth – in those diffuse. In spite of the tumour progression, a number of neoplastic cells may retain initial caryotypical and immunologic markers.

MULTI-STEP TRANSFORMATION OF LYMPHOID CELLS



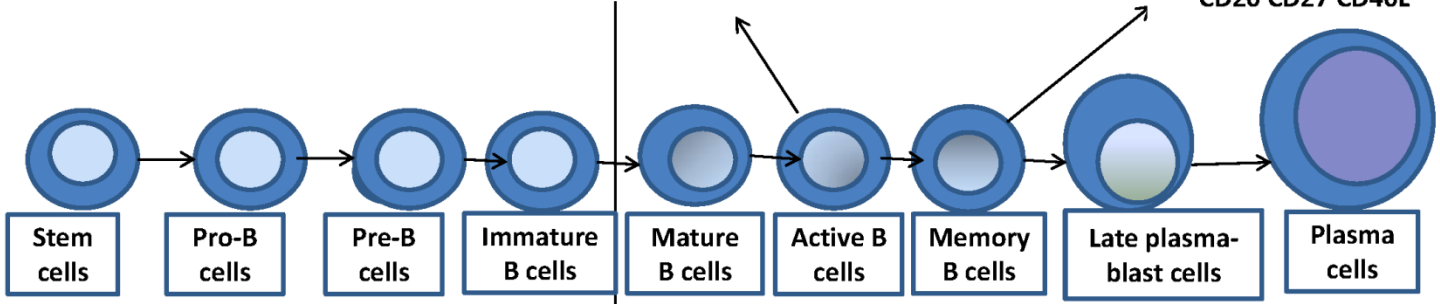
Bone marrow
Antigen Independent



Peripheral Lymphoid tissue
Antigen Dependent Phase

Short lived
Plasma cells

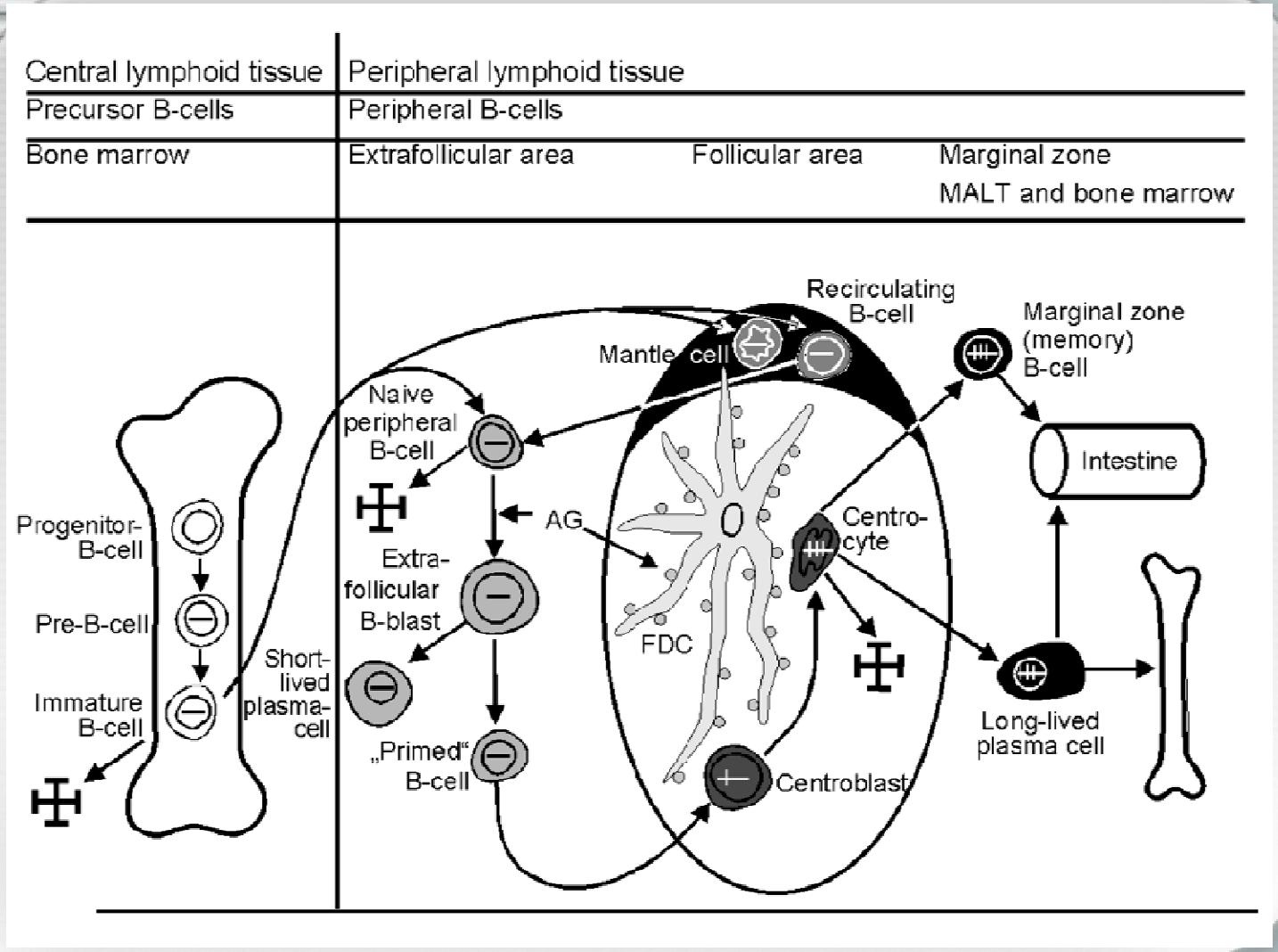
Early Plasma-blast
CD20 CD27 CD40L



Cell Surface Antigens	
CD19	← →
CD20	← → •
CD27	← → •
Serum BAFF and CD38	← → •
CD138	← → •

EVENTS IN B-CELL DEVELOPMENT

(American Society of Hematology, New Approaches to Lymphoma Diagnosis. Hematology 2001)



EVENTS IN B-CELL DEVELOPMENT

(American Society of Hematology, New Approaches to Lymphoma Diagnosis. Hematology 2001)

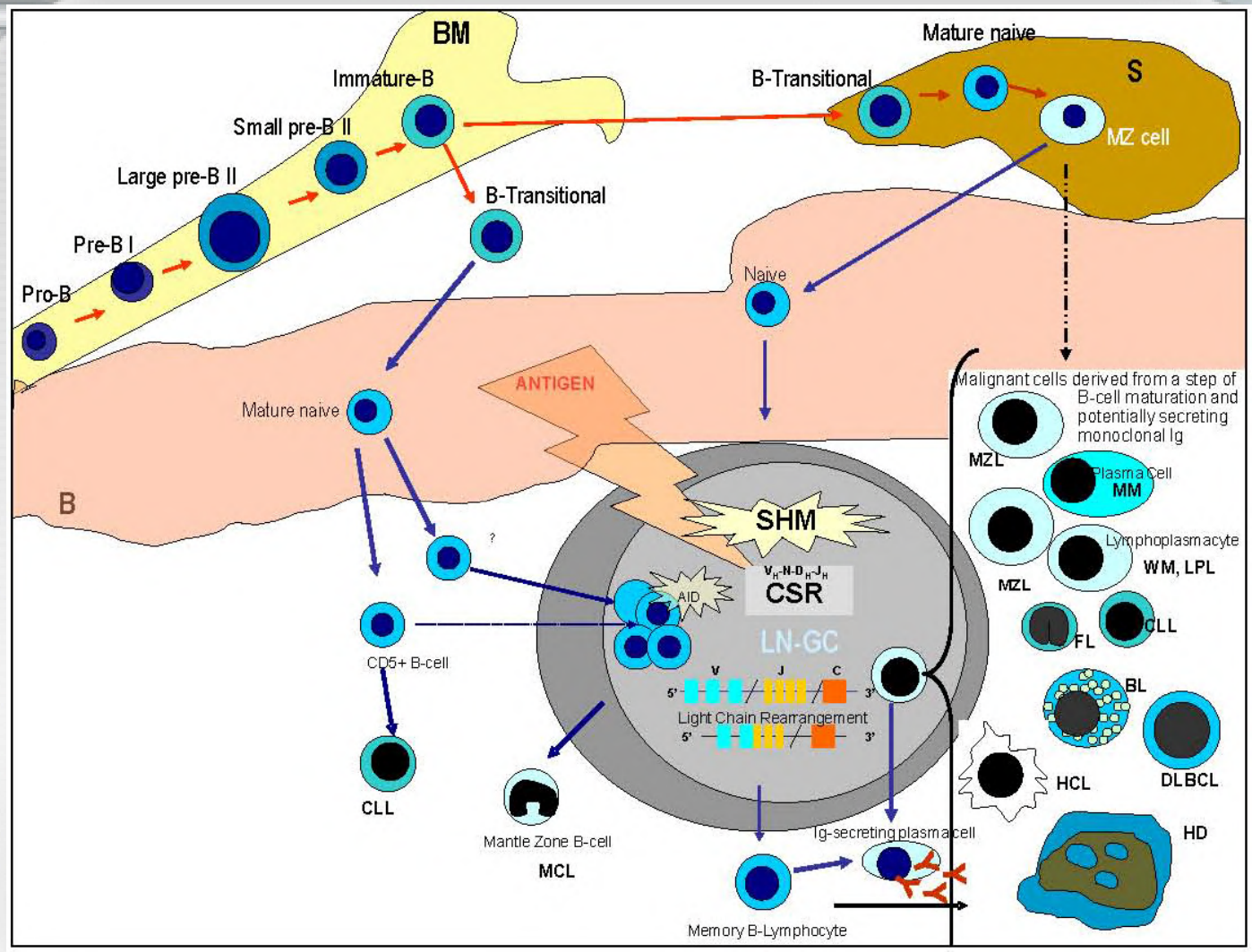
The development and maturation process of B cells begins in the bone marrow. Here, the "pre-B cell" arises from the "progenitor (Pro) B cell" following rearrangement of the immunoglobulin heavy chain gene (symbolized with horizontal lines in black). Subsequently, rearrangement of the light chain genes occurs resulting in the expression of the whole immunoglobulin molecule on the cell surface, serving as an antigen receptor. With the production of this "immature" B cell, the initial phase of B-cell development is, thereby, completed. The "immature" B cell is so defined since it is unable to initiate an immune response following the presentation of a foreign antigen. The B-cell attains this ability only on leaving the bone marrow, passing through the blood stream and entering the peripheral lymphoid tissue. Here, the B cell migrates to the outer region of the lymph node in the "primary" follicles and, later, to the follicle mantles. This differentiation step is associated with the additional expression of IgD. These IgM+/IgD+ B cells are known as "naive mature B-cells". When these cells come into contact with antigen (AG), which can bind to their immunoglobulin molecules, they transform into proliferating extrafollicular B blasts, from which short-lived plasma cells and "antigen-induced" or "primed" B cells are derived. These "primed" B cells initiate and maintain the germinal center reaction, during which they transform into rapidly proliferating centroblasts. During the mitotic proliferation and differentiation of the centroblasts into centrocytes, somatic mutations in the variable region of the immunoglobulin genes are inserted in a randomized manner (the mutations are represented by vertical lines). The centrocytes with advantageous mutations (i.e. those which lead to an increase in the affinity of the immunoglobulin receptor) differentiate further, passing out of the germinal centre into long-lived plasma cells or into "memory" B cells. The latter remain in the marginal zone. FDC, folicular dendritic cell; ⊹, apoptosis

As a result of the differentiation phases of B-cells and of the somatic mutation process, 3 major different mature forms of B-cells can be identified:

- Naive mature B-cells (recirculating and sessile subtypes)
- Germinal center B-cells (centroblasts and centrocytes)
- Post germinal center B-cells which include memory B cells and long-lived plasma cells

From all of these different B-cell forms, malignant B-cell lymphomas arise, which distinguish themselves clinically and which are characterized in their biological behavior not only by the transformation event but also by the inherent characteristics of the cell of origin. Classical Hodgkin lymphomas, in which the phenotypical and clinical features are predominantly determined by the transformation event, are an exception to this rule.

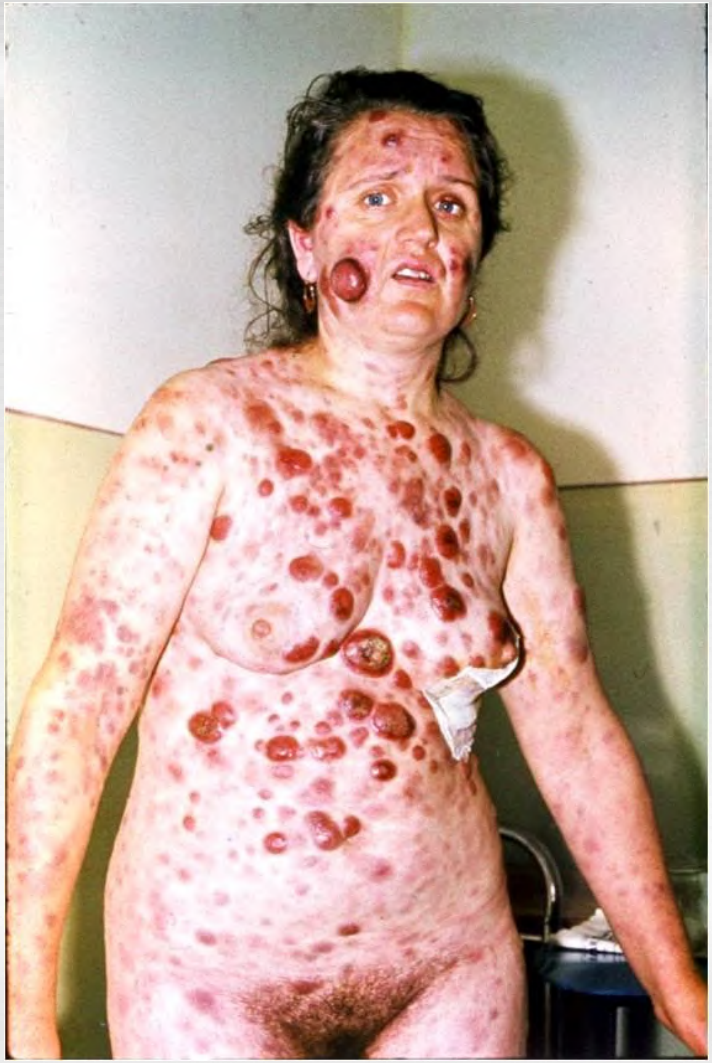
MULTI-STEP TRANSFORMATION OF LYMPHOID CELLS



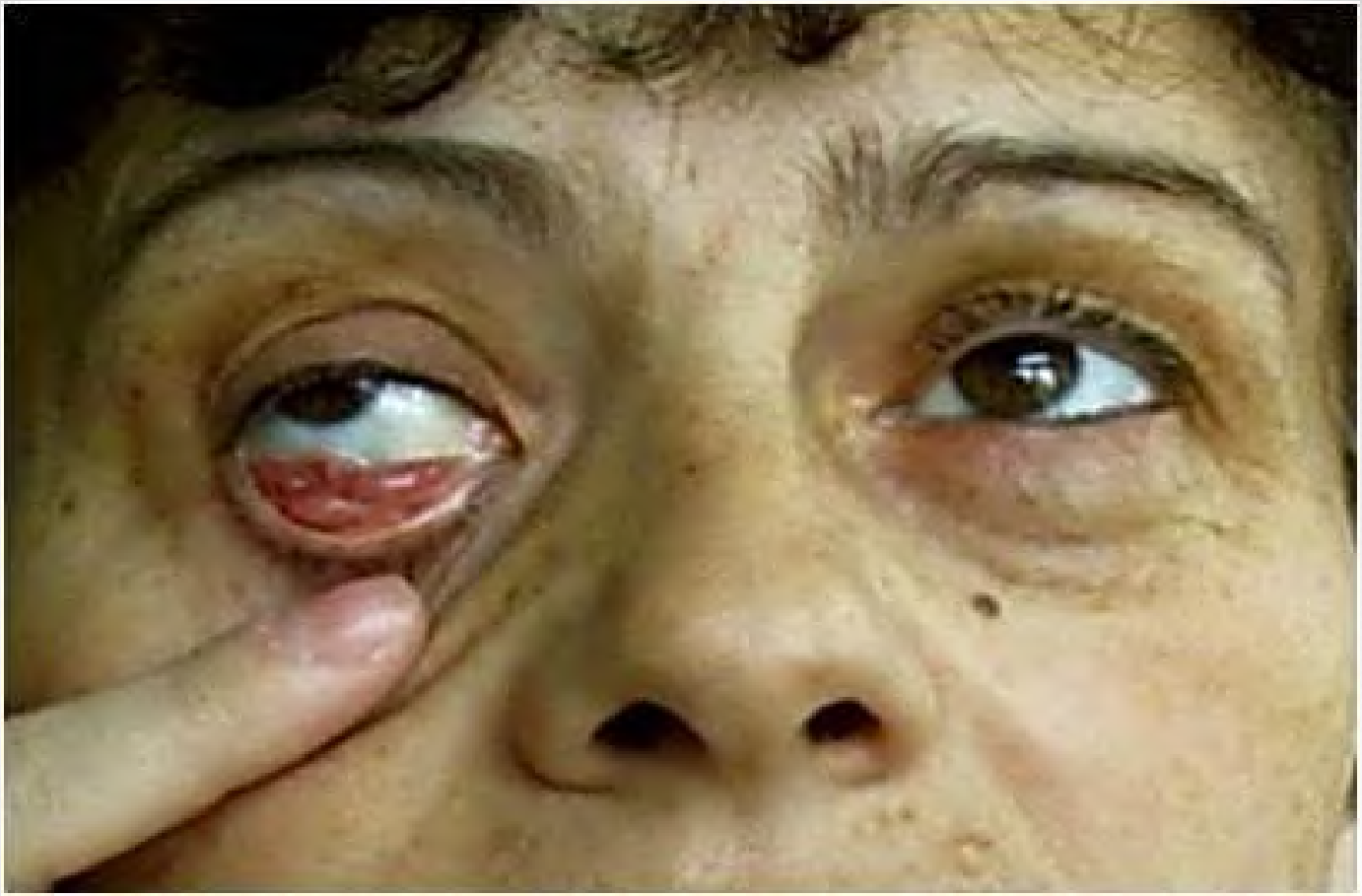
LOCALIZATIONS OF PRIMARY TUMOR FOCUS IN NON-HODGKIN LYMPHOMAS

Localizarea primară	*Numărul de bolnavi*	
	Abs.	*%*
Ganglionii limfatici	**260**	**51,0**
periferici	**173**	**33,9**
mediastinali	**12**	**2,4**
retroperitoneali şi abdominali	**39**	**7,6**
grupa neidentificată	**36**	**7,1**
Localizări extranodale	**214**	**42,0**
inelul Waldayer	**80**	**15,7**
tractul gastrointestinal	**68**	**13,3**
splina	**21**	**4,1**
oasele, pielea, ţesuturile moi	**23**	**4,5**
plămâni, pleura	**2**	**0,4**
glanda mamară	**4**	**0,8**
alte localizări	**16**	**3,2**
nu a fost identificată	**36**	**7,0**
Total	**510**	**100,0**

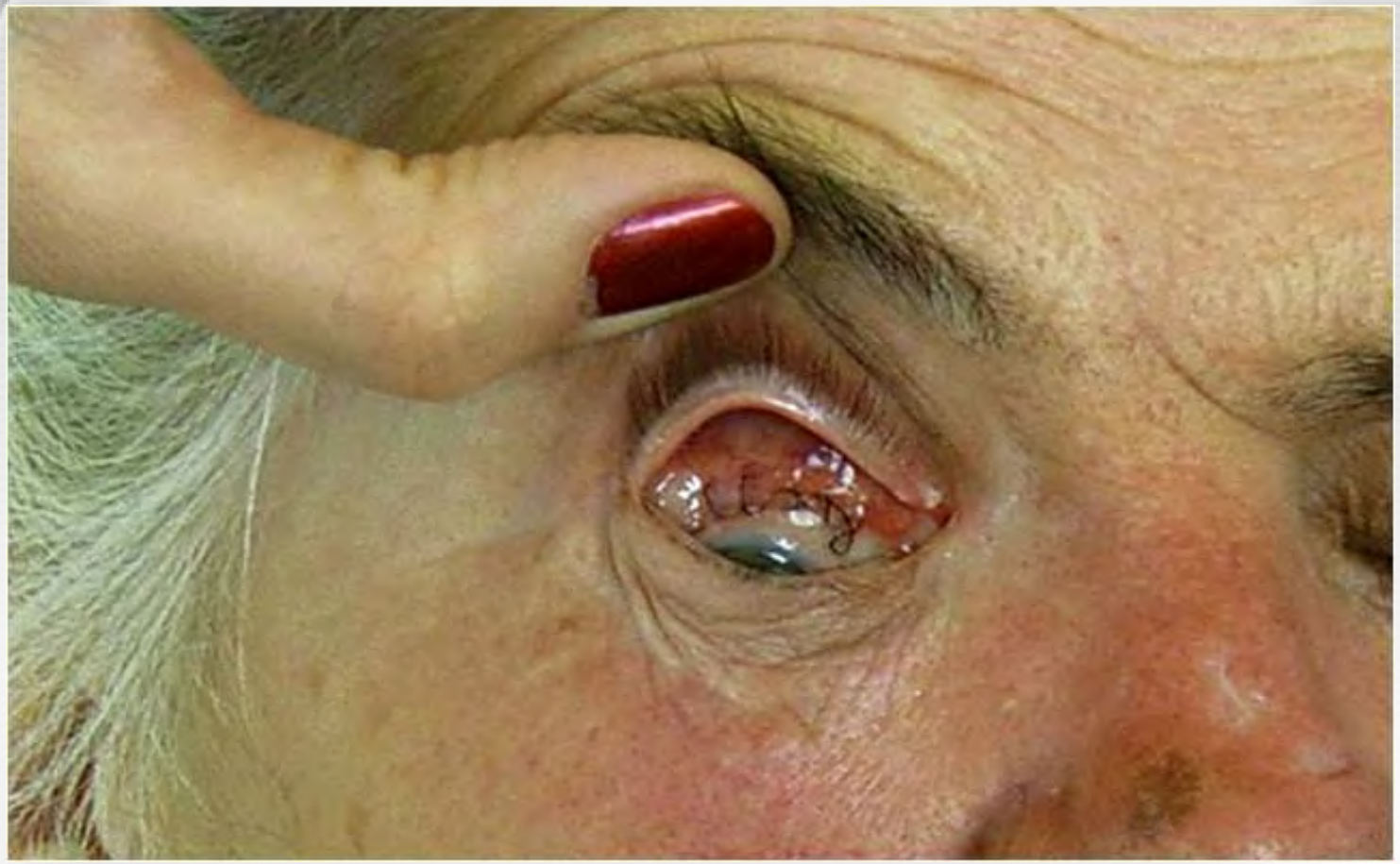
PRIMARY CUTANEOUS NON-HODGKIN LYMPHOMA



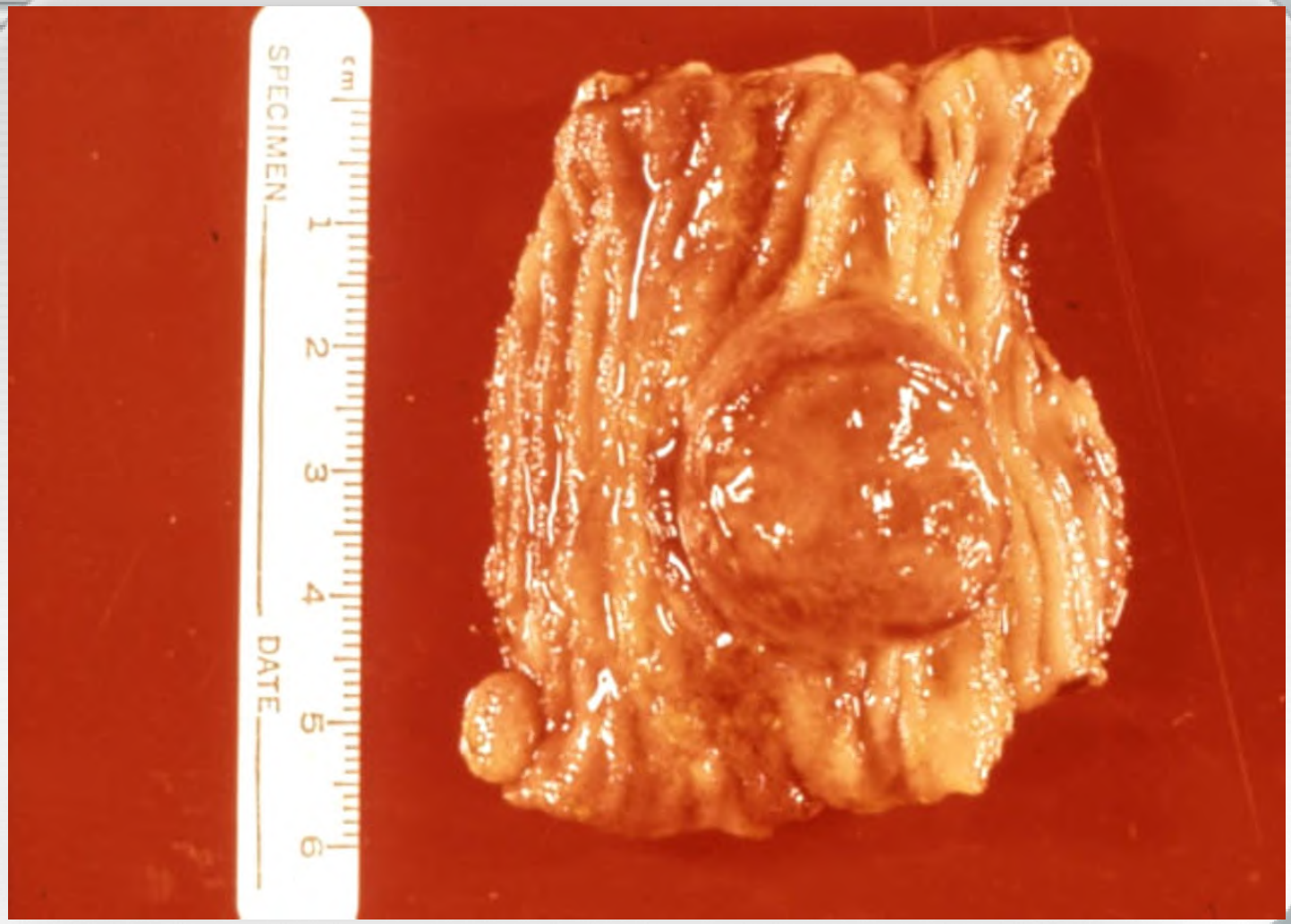
PRIMARY EYELID NON-HODGKIN LYMPHOMA



PRIMARY EYELID NON-HODGKIN LYMPHOMA

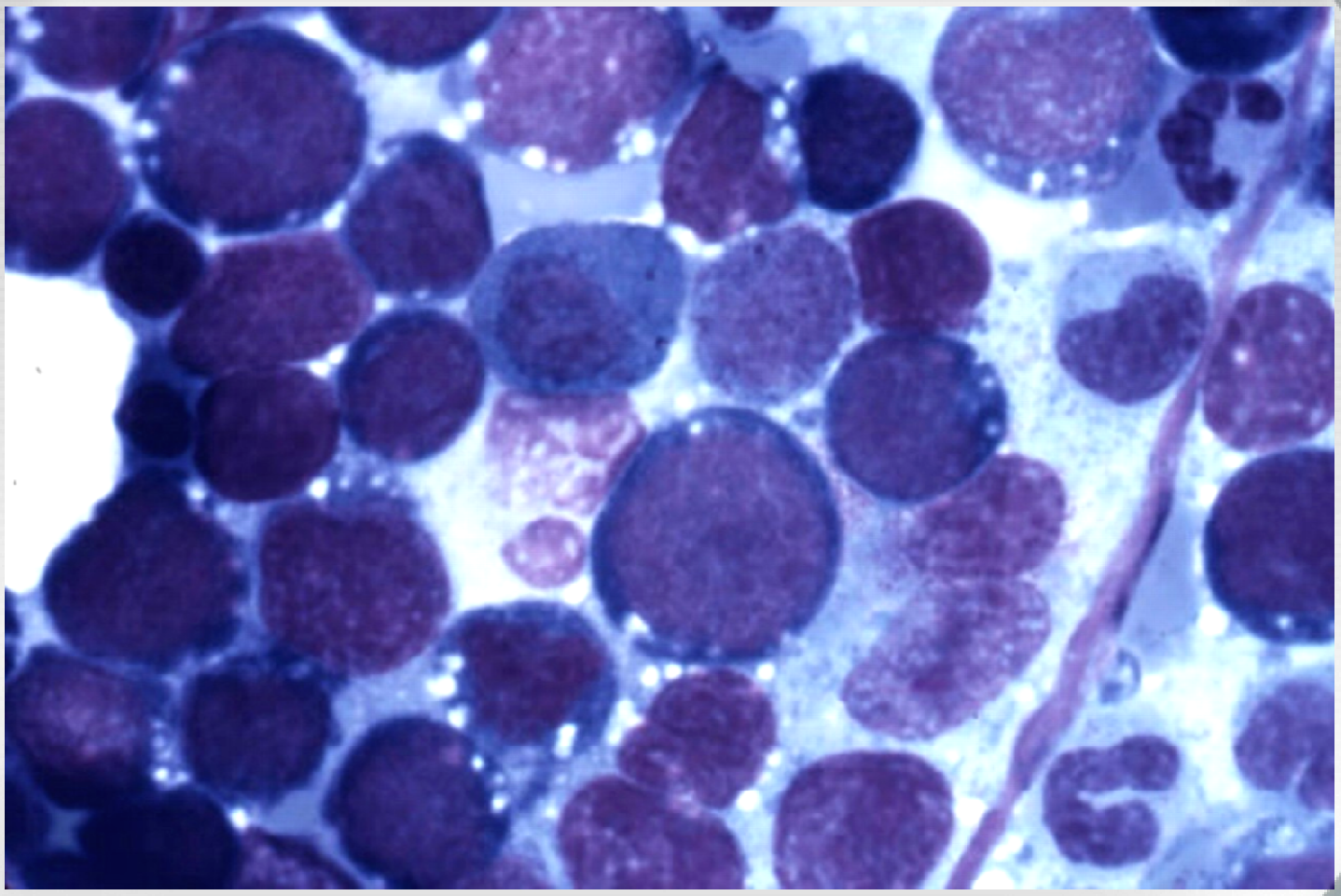


NON-HODGKIN LYMPHOMA, BURKITT TYPE



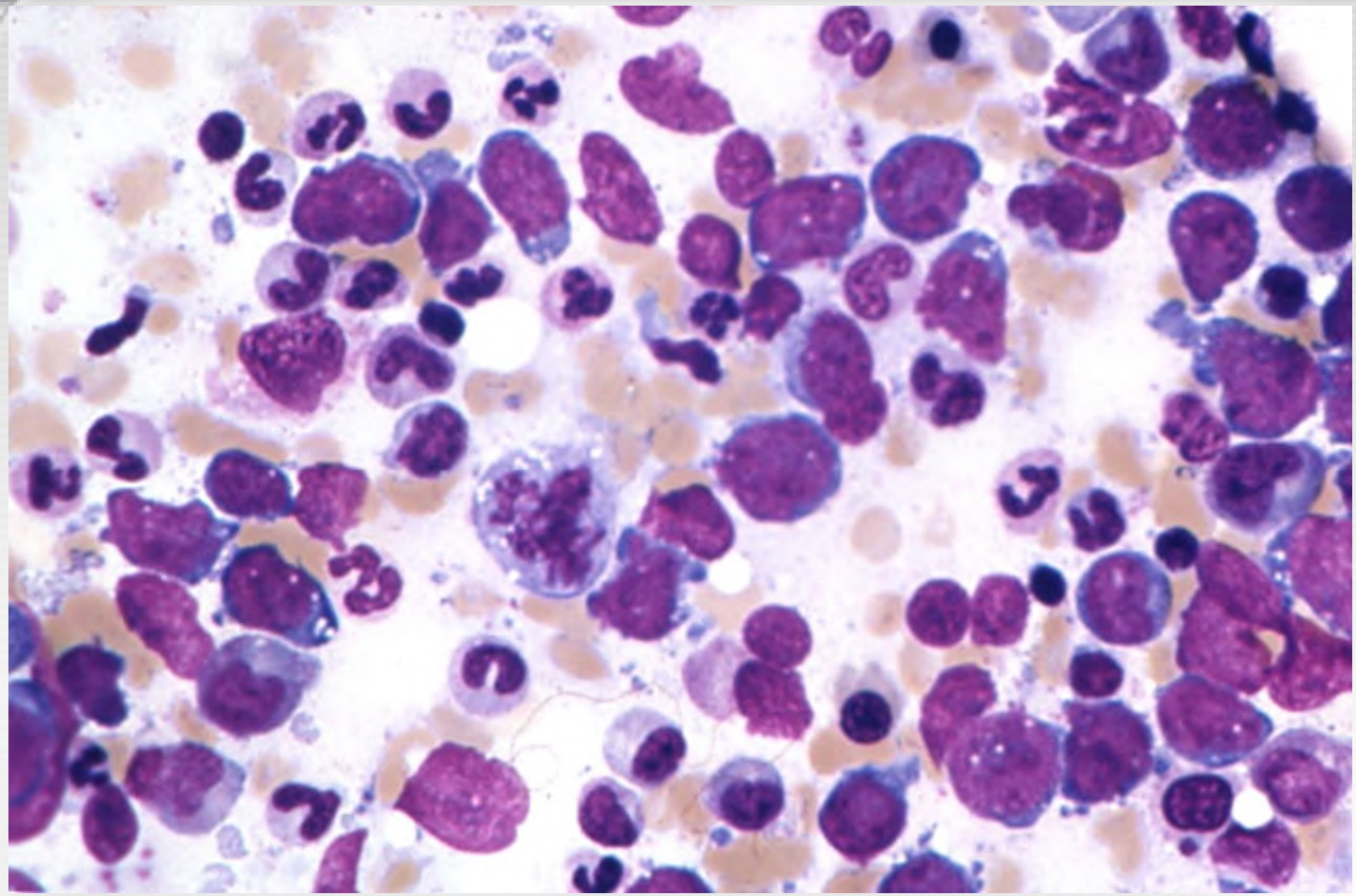
Obstruction lesion in ileum, a common presenting clinical feature in sporadic Burkitt lymphoma

NON-HODGKIN LYMPHOMA, BURKITT TYPE



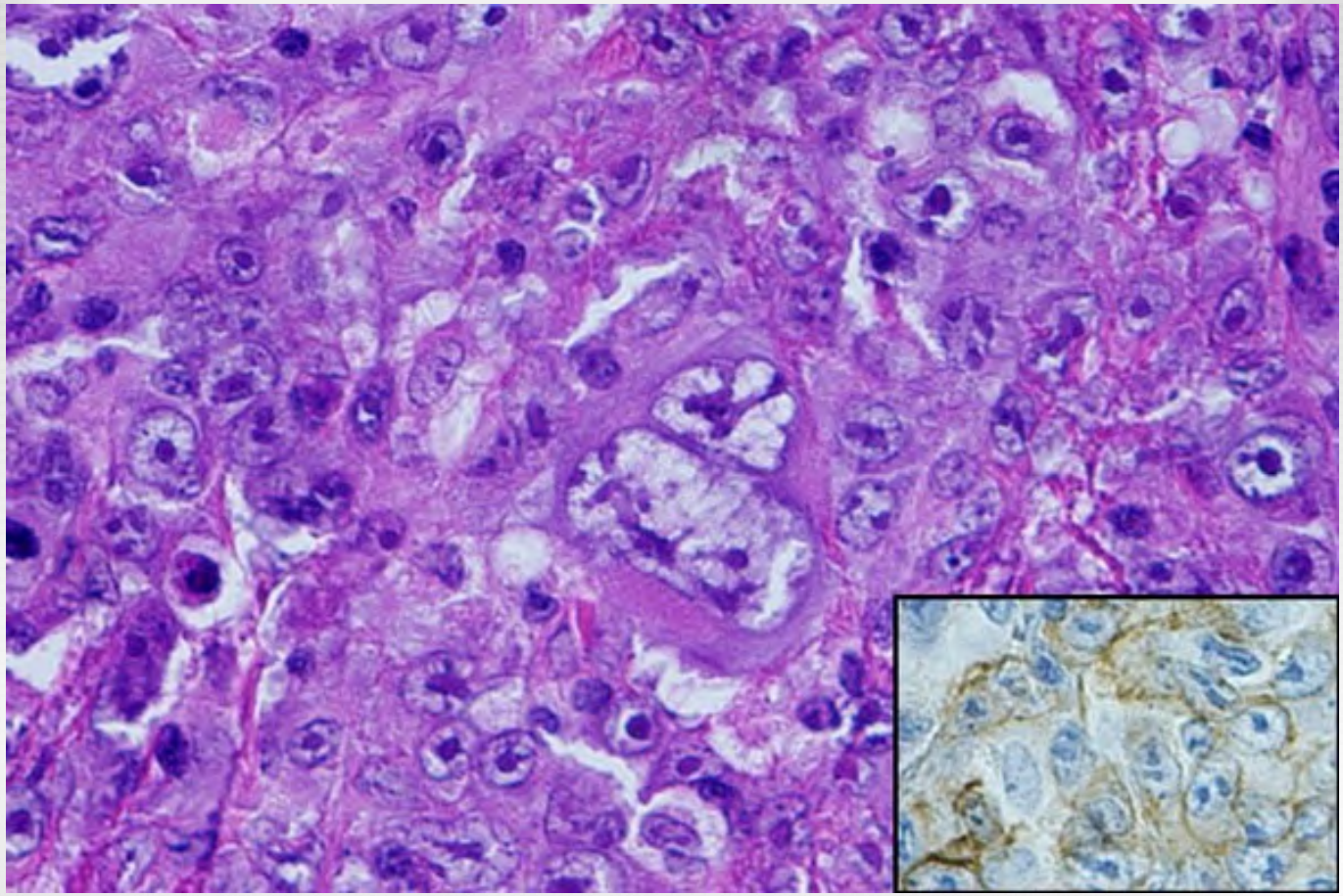
Cytology showing deeply basophilic vacuolated cytoplasm - vacuoles contain lipid.
May-Giemsa staining, x 1000.

NON-HODGKIN LYMPHOMA, BURKITT TYPE



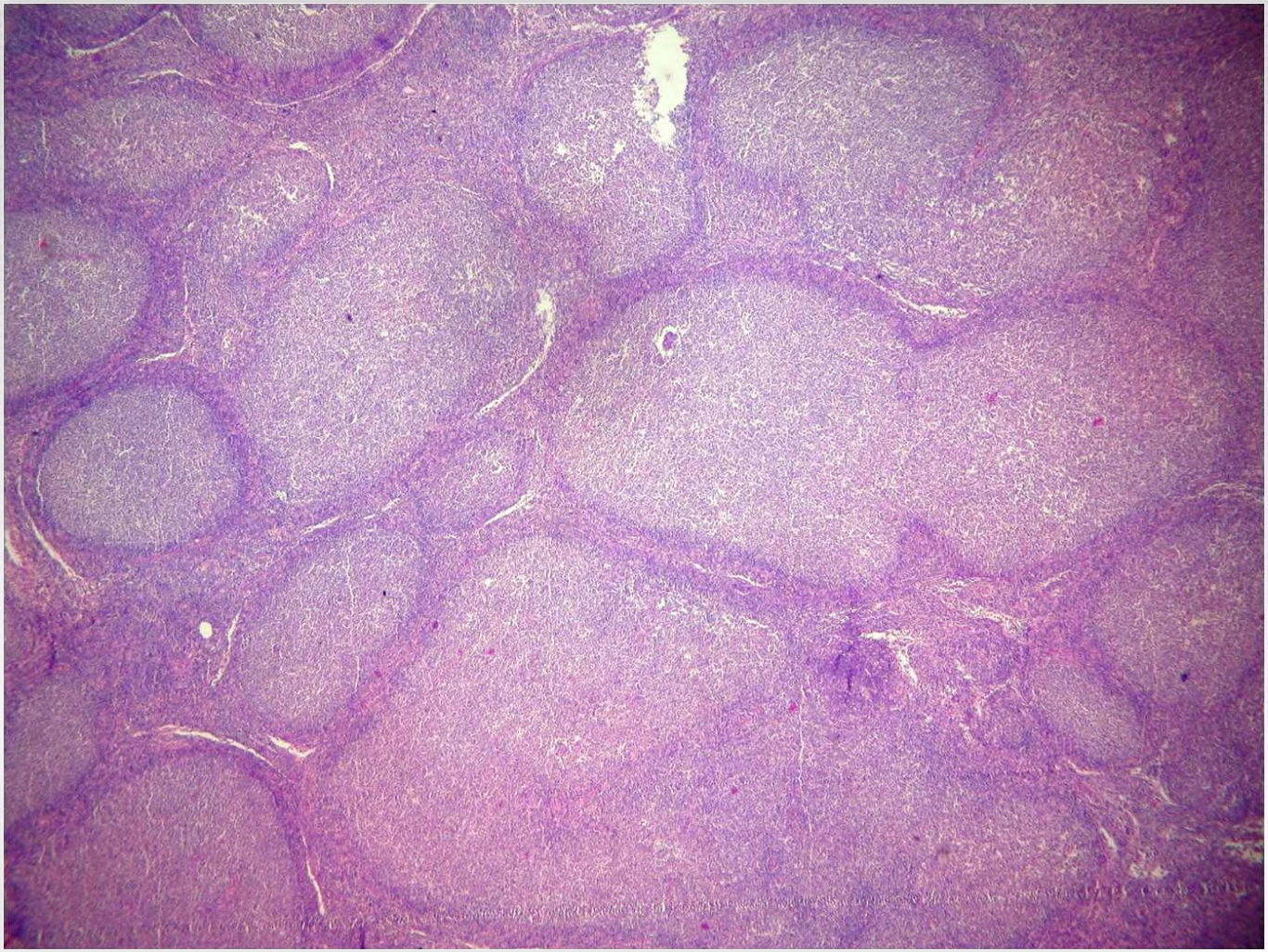
Bone marrow aspirate with admixture of Burkitt lymphoma cells.
May-Giemsa staining, x 1000.

DIFFUSE LARGE B-CELL NON-HODGKIN LYMPHOMA, ANAPLASTIC TYPE



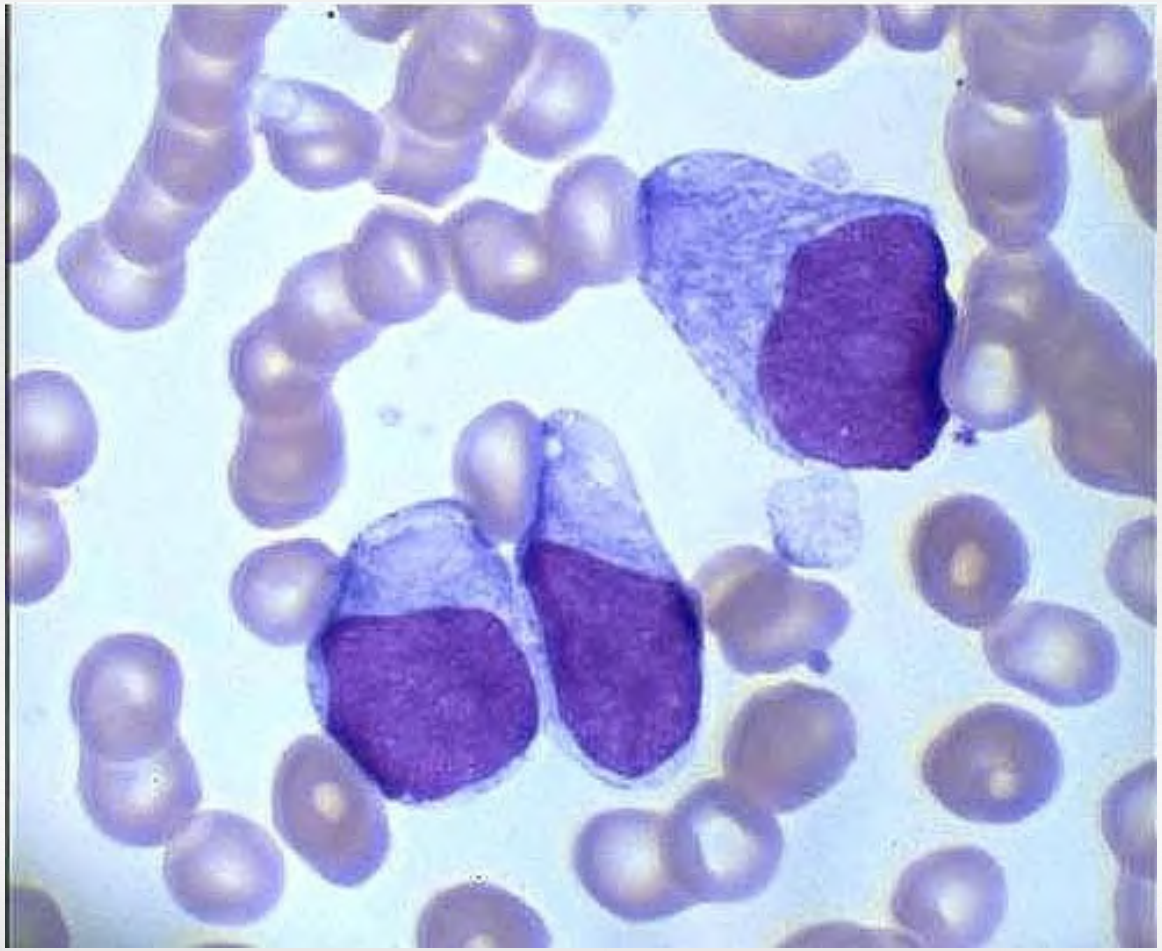
Lymph node biopsy.
Hematoxylin and eosin stain, x1000.

FOLLICULAR NON-HODGKIN LYMPHOMA



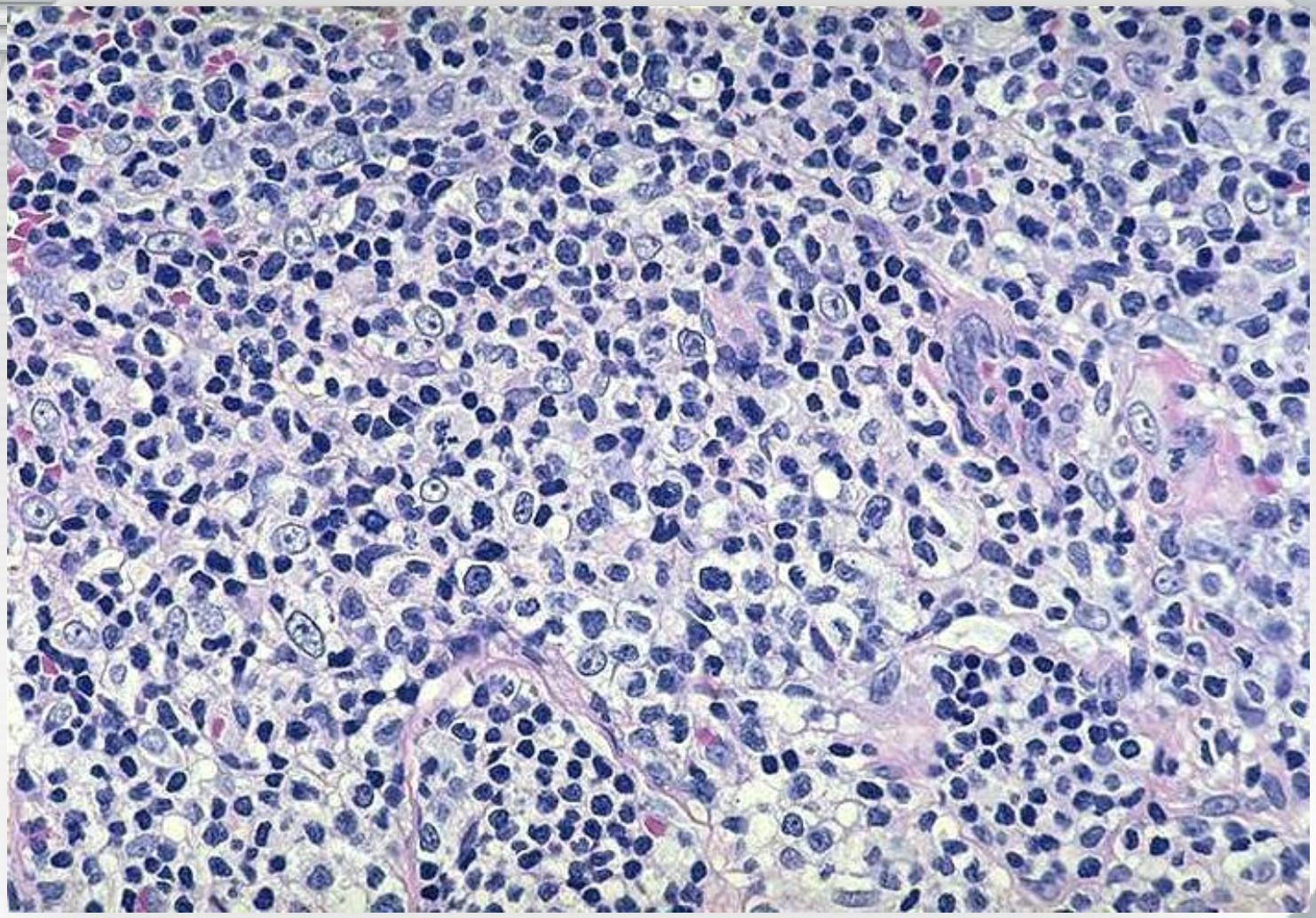
May-Giemsa staining, x 100

***BONE MARROW SMEAR IN** NON-HODGKIN LYMPHOMA*



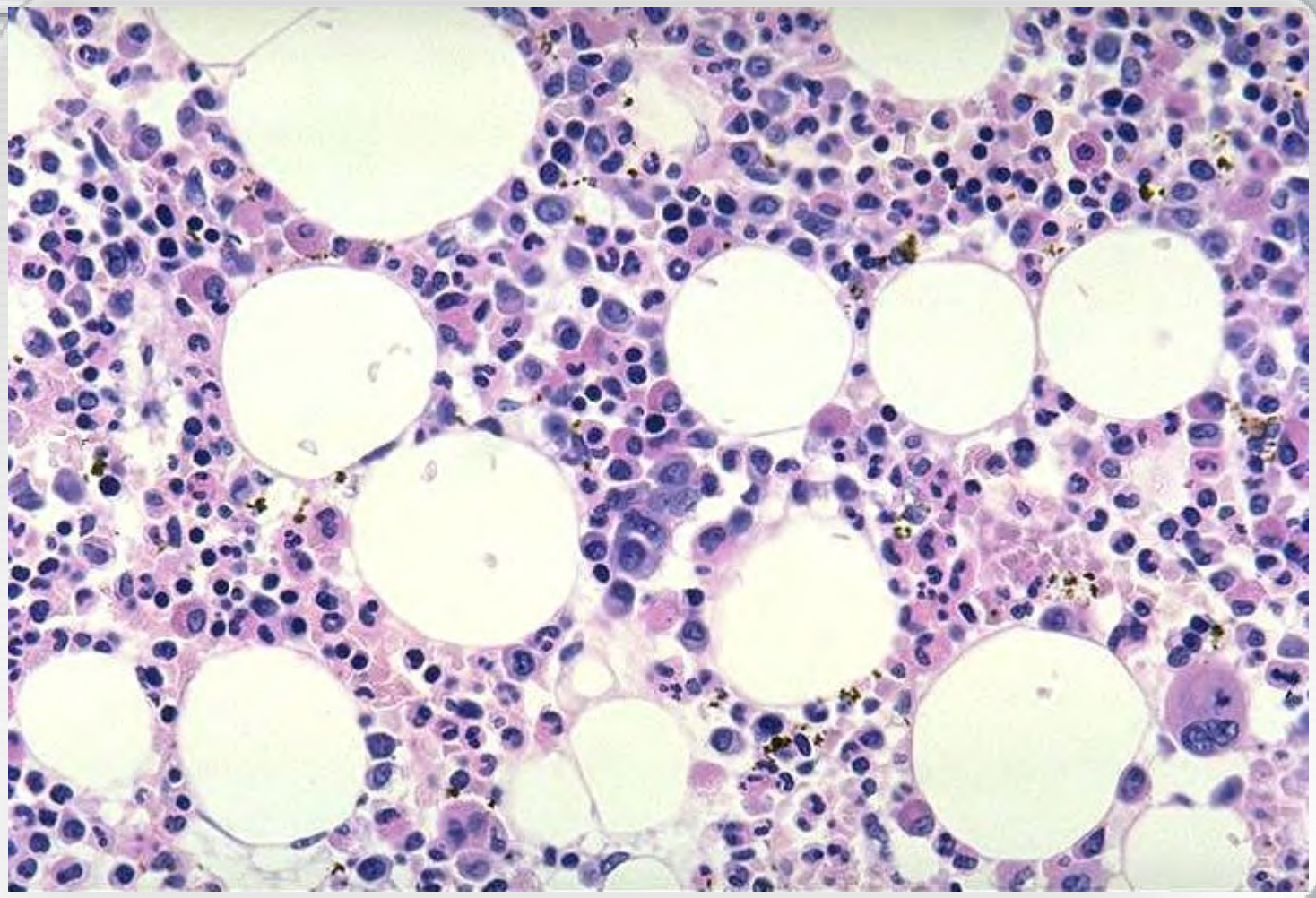
May-Giemsa staining, x 1000

CUTANEOUS T-CELL NON-HODGKIN LYMPHOMA



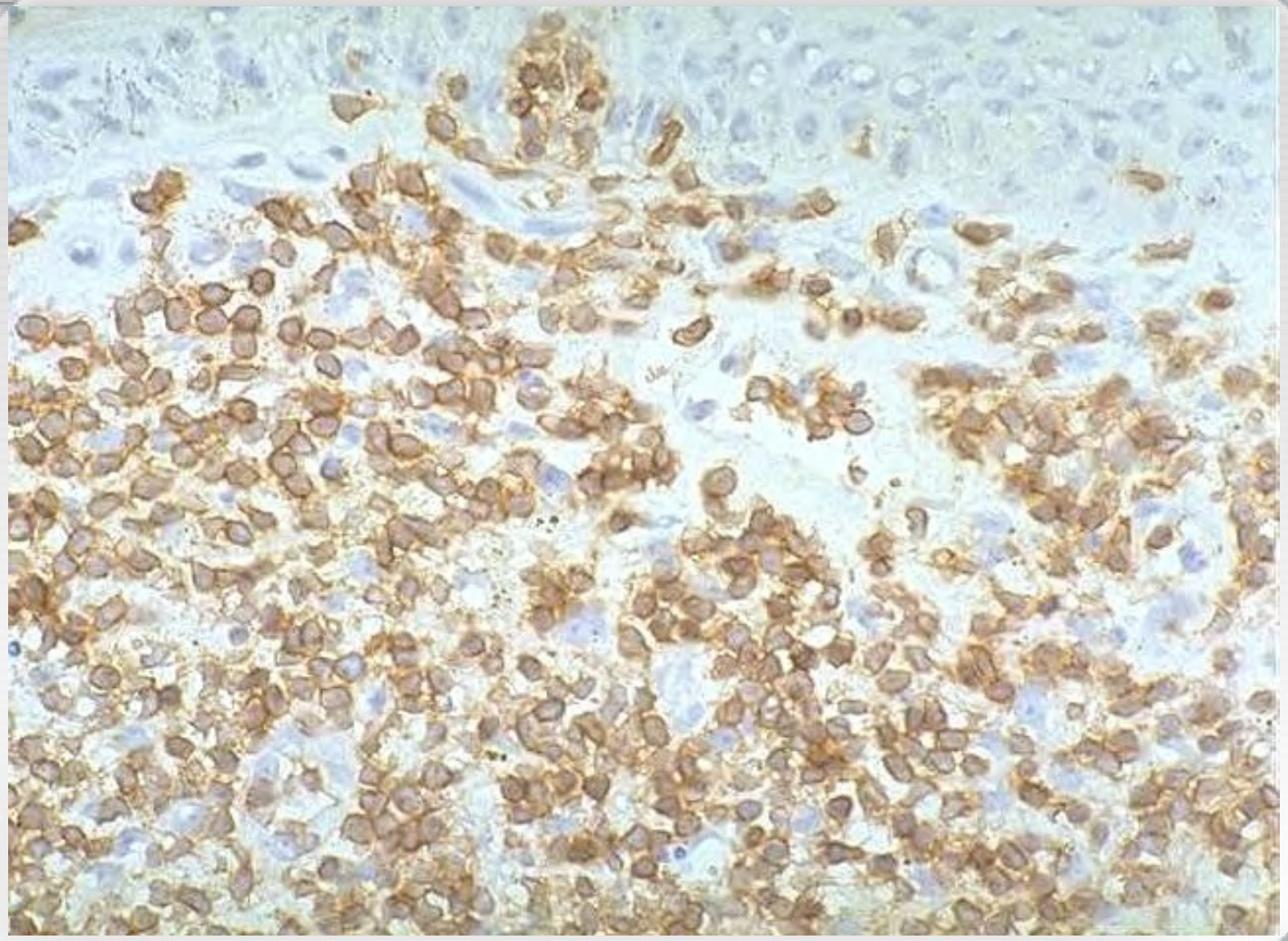
Hematoxylin and eosin stain, x400

CUTANEOUS T-CELL NON-HODGKIN LYMPHOMA



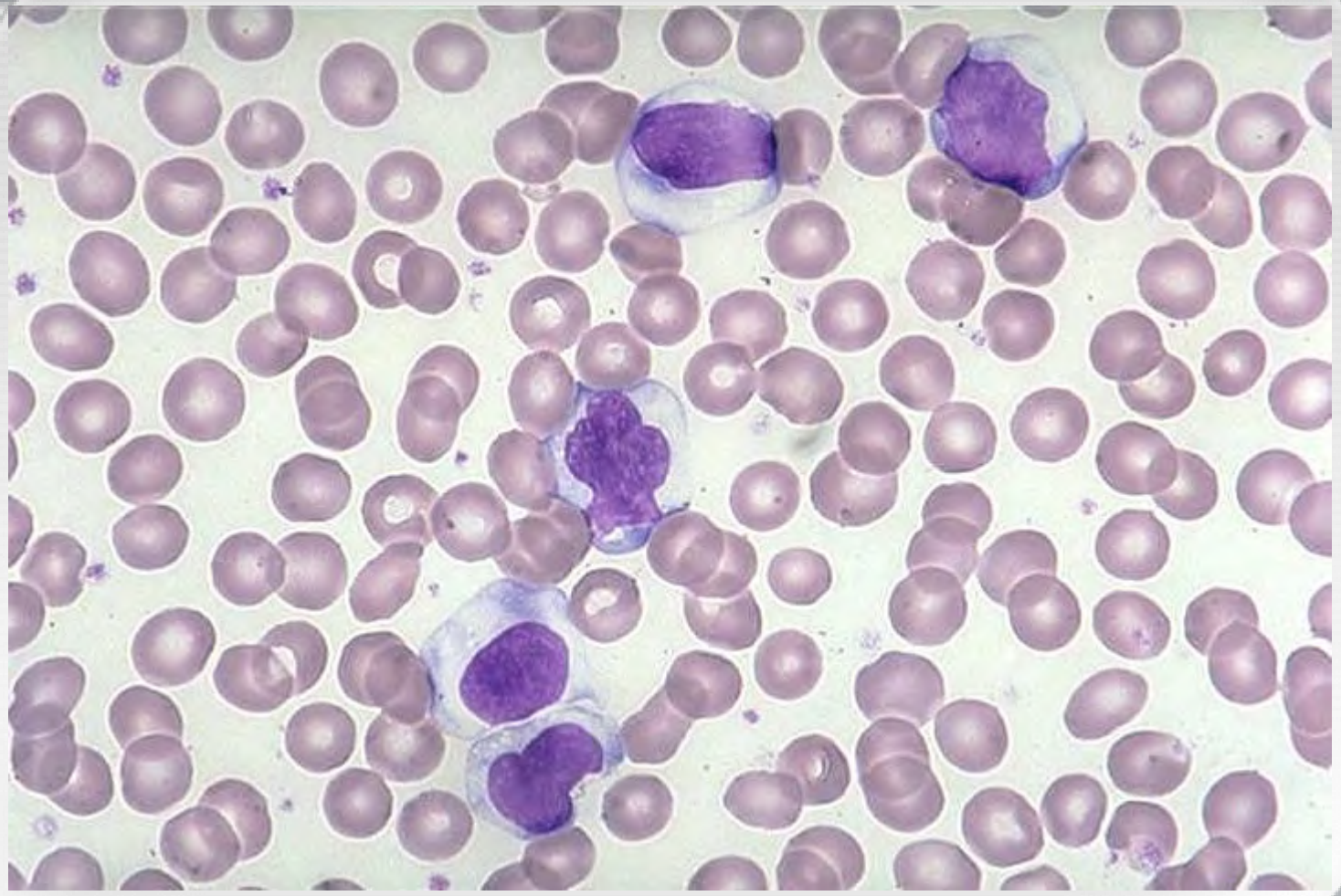
Clot section.
Hematoxylin and eosin stain, x400.

CUTANEOUS T-CELL NON-HODGKIN LYMPHOMA



Immunostain_antibody CD3(Leu4), x400

CUTANEOUS T-CELL NON-HODGKIN LYMPHOMA



Blood smear.
May-Giemsa stain, x1000.

IMMUNOPHENOTYPIC AND GENETIC FEATURES OF COMMON B-CELL NEOPLASMS

(American Society of Hematology, New Approaches to Lymphoma Diagnosis. Hematology 2001)

Neoplasm	SIg; cIg	CD5	CD10	Bcl6	CD23	CD43	CD103	Cyclin D1	CD 138	Genetic Abnormality	Immuno-globulin Genes*
B-SLL/CLL	+; -/+	+	-	-	+	+	-	-	-	trisomy 12; 13q	R,U (50%); M (50%)
Lymphoplasmacytic lymphoma	+; +	-	-	-	-	+/-	-	-	-/+	t(9;14); del 6(q23)	R,M
Hairy cell leukemia	+;-	-	-	-	-	+	++	+/-	-	none known	R,M
Plasma cell myeloma	-;+	-	-/+	-	-	-/+	-	-/+	+	t(4:14), t(6;14) t(14;16), t(1;14)	R,M
Splenic marginal zone lymphoma	+; -/+	-	-	-	-	-	+	-	-	none known	R,M
Follicular lymphoma	+; -	-	+/-	+	-/+	-	-	-	-	t(14;18); bcl-2	R,M,O
Mantle cell lymphoma	+; -	+	-	-	-	+	-	+	-	t(11;14); bcl-1	R,U
MALT lymphoma	+; +/-	-	-	-	-/+	-/+	-	-	-	+3, t(11;18); API2/MLT1	R,M,O
Diffuse large B-cell lymphoma	+/-; -/+	-	-/+	+/-	NA	-/+	NA	-	-/+	t(14;18),t(8;14) 3q27; BCL2, cMYC, BCL6	R,M
Burkitt lymphoma	+; -	-	+	+	-	-	NA	-	-	t(8;14), t(2;8), t(8;22); cMYC; EBV-/+	R,M

Abbreviations: R, rearranged; M, mutated; NK, natural killer cell; U, unmutated; O, ongoing mutations; NA, not available

Key: + = >90% positive; +/- = > 50% positive; -/+ = < 50% positive; - = < 10% positive

IMMUNOPHENOTYPIC AND GENETIC FEATURES OF COMMON T-CELL NEOPLASMS

(American Society of Hematology, New Approaches to Lymphoma Diagnosis. Hematology 2001)

Neoplasm	CD3 (S;C)	CD5	CD7	CD4	CD8	CD30	TCR	NK[16, 56]	Cytotoxic granule
T-prolymphocytic leukemia	+	-	+,+	+/-	-/+	-	αβ	-	-
T-large granular lymphoproliferative disease	+	-	+,+	-	+	-	αβ	+,-	+
NK large granlular lymphoproliferative disease	-	-	+, -	-	+/-	-	-	-,+	+
Extranodal NK/T-cell lymphoma	-;+	-	-/+	-	-	-	-	NA,+	+
Hepatosplenic T-cell lymphoma	+	-	+	-	-	-	γδ>>αβ	+,-/+	+
Enteropathy-type T-cell lymphoma	+	+	+	-	+/-	+/-	αβ>>γδ	-	+
Mycosis fungoides	+	+	-/+	+	-	-	αβ	-	-
Cutaneous anaplastic large cell lymphoma	+	+/-	+/-	+/-	-	++	αβ	-	-/+
Subcutaneous panniculitis-like T-cell	+	+	+	-	+	-/+	αβ>γδ	-,+/-	+
Peripheral T-cell lymphoma, unspecified	+/-	+/-	+/-	+/-	-/+	-/+	αβ>γδ	-/+	-/+
Angioimmunoblastic	+	+	+	+/-	-/+	-	αβ	-	NA
Primary systemic anaplastic large cell lymphoma	+/-	+/-	NA	-/+	-/+	++	αβ	-	+

Abbreviations: R, rearranged; M, mutated; NK, natural killer cell; U, unmutated; O, ongoing mutations; TCR, T-cell receptor gene; Ig, immunoglobulin; NA, not available

Key: + = >90% positive; +/- = > 50% positive; -/+ = < 50% positive; - = < 10% positive; Cytotoxic granule = TIA-1, perforin, and/or granzyme

* Mutations in the Ig gene V region indicate exposure to antigen.

INTERNATIONAL PROGNOSTIC INDEX AND AGE-ADJUSTED INDEX FOR AGGRESSIVE LYMPHOMA PATIENTS TREATED WITH DOXORUBICIN-CONTAINING COMBINATION CHEMOTHERAPY

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)

IPI: Risk factors:

- Age >60 years
- LDH > normal
- ECOG performance status 2–4
- Stage III or IV
- Two or more extranodal sites of disease

Risk group	Risk factors (Sum)	CR (%)	5-year OS (%)
Low	0–1	87	73
Low-intermediate	2	67	51
High-intermediate	3	55	43
High	4–5	44	26

Age-adjusted IPI for age <60 years:

Risk factors:

- LDH > normal
- Performance status 2–4
- Stage III–IV

Low	0	92	83
Low-intermediate	1	78	69
High-intermediate	2	57	46
High	3	46	32

From Shipp. Blood 1994;83:1165–73.

CR = complete response; ECOG = Eastern Cooperative Oncology Group; OS = overall survival.

CHEMOTHERAPY REGIMENS, COMMONLY USED IN NON-HODGKIN LYMPHOMAS

(Williams M.E., Kahn M.J., American Society of Hematology Self-Assessment Program. Blackwell Publishing: 2005)

Newly diagnosed patients	Relapsed and refractory patients
CVP:	ICE:
Cyclophosphamide	Ifosfamide
Vincristine	Carboplatin
Prednisone	Etoposide
CHOP:	DHAP:
CVP plus doxorubicin	Dexamethasone
R-CHOP:	High-dose araC
CHOP plus rituximab	*Cis*-platinum
MACOP-B:	ESHAP:
Methotrexate/leucovorin	Etoposide
Doxorubicin	Methylprednisolone
Cyclophosphamide	High-dose araC
Vincristine	*Cis*-platinum
Prednisone	EPOCH:
Bleomycin	Etoposide*
M-BACOD:	Vincristine*
Methotrexate/leucovorin	Doxorubicin*
Bleomycin	Cyclophosphamide
Doxorubicin	Prednisone
Cyclophosphamide	
Vincristine	
Dexamethasone	
ProMACE-CytaBOM:	
Prednisone	
Doxorubicin	
Cyclophosphamide	
Etoposide	
Cytosine arabinoside (araC)	
Bleomycin	
Vincristine	
Methotrexate/leucovorin	

*Continuous infusion × 4 days/cycle.

COMBINATION CHEMOTHERAPY IN NON-HODGKIN LYMPHOMAS: REGIMENS, MODE OF ADMINISTRATION AND DOSES

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)

Regimen	Dose	Route and frequency
CVP ± Rituximab		
Cyclophosphamide	400 mg/m^2	750-1,000 mg/m^2 on day 1
Vincristine	1.4 mg/m^2	IV on day 1 (maximum, 2 mg)
Prednisone	100 mg or 100 mg/m^2	PO on days 1-5
Rituximab	375 mg/m^2	IV on day 1
Repeat treatment every 21 days.		
CHOP ± Rituximab		
Cyclophosphamide	750 mg/m^2	IV on day 1
Doxorubicin HCl	50 mg/m^2	IV on day 1
Oncovin	1.4 mg/m^2	IV on day 1 (maximum, 2 mg)
Prednisone	40 mg/m^2 or 100 mg/day or 100 mg/m^2/day	PO on days 1-5
Repeat treatment every 21 days.		
CHOEP ± Rituximab		
Cyclophosphamide	750 mg/m^2	IV on day 1
Doxorubicin	50 mg/m^2	IV on day 1
Etoposide	100 mg/m^2	IV on days 1-3
Oncovin	1.4 mg/mL	IV on day 1 (maximum, 2 mg)
Prednisone	100 mg	PO on days 1-5
Rituximab	375 mg/m^2	IV on day 1
Repeat treatment every 21 days.		
C-MOPP		
Cyclophosphamide	650 mg/m^2	IV on days 1, 8
Oncovin	1.4 mg/m^2	IV on days 1, 8
Procarbazine	100 mg/m^2	PO on days 1-14
Prednisone	40 mg	PO on days 1-14
Repeat treatment every 28 days.		
MACOP-B		
Methotrexate[a]	400 mg/m^2	IV on weeks 2, 6, 10
Adriamycin	50 mg/m^2	IV on weeks 1, 3, 5, 7, 9, 11
Cyclophosphamide	350 mg/m^2	IV on weeks 1, 3, 5, 7, 9, 11
Oncovin	1.4 mg/m^2	IV on weeks 2, 4, 6, 8, 10, 12 (maximum, 2 mg)
Prednisone	75 mg	PO daily for 12 weeks; dose tapered over the last 15 days
Bleomycin	10 U/m^2	IV on weeks 4, 8, 12
Co-trimoxazole	2 tablets	PO twice daily throughout

COMBINATION CHEMOTHERAPY IN NON-HODGKIN LYMPHOMAS: REGIMENS, MODE OF ADMINISTRATION AND DOSES

(Pazdur R., Coia L.R., Hoskins W.J. et al., Cancer Management: A Multidisciplinary Approach. 8th Edition. New York: CMP Healthcare Media)

Regimen	Dose	Route and frequency
FND		
Fludarabine	25 mg/m^2	IV on days 1-3
Novantrone	10 mg/m^2	IV on day 1
Dexamethasone	20 mg	PO/IV on days 1-5
Repeat treatment every 21-28 days depending on hematologic recovery.		
ProMACE-CytaBOM		
Cyclophosphamide	650 mg/m^2	IV on day 1
Etoposide	120 mg/m^2	IV on day 1
Adriamycin	25 mg/m^2	IV on day 1
Cytarabine	300 mg/m^2	IV on day 8
Bleomycin	5 U/m^2	IV on day 8
Oncovin	1.4 mg/m^2	IV on day 8 (maximum, 2 mg)
Methotrexate	120 mg/m^2	IV on day 8
Leucovorin	25 mg/m^2	PO q6h for 4 doses; start 24 hours after methotrexate
Prednisone	60 mg	PO on days 1-14
Co-trimoxazole	2 tablets	PO twice daily throughout
Repeat treatment every 28 days.		
ProMACE-MOPP		
Cyclophosphamide	650 mg/m^2	IV on day 1
Etoposide	120 mg/m^2	IV on day 1
Adriamycin	25 mg/m^2	IV on day 1
Procarbazine	100 mg/m^2	PO on days 8-14
Mechlorethamine	6 mg/m^2	IV on day 8
Oncovin	1.4 mg/m^2	IV on day 8 (maximum, 2 mg)
Prednisone	60 mg	PO on days 1-14
Methotrexate	500 mg/m^2	IV on day 15
Leucovorin	50 mg/m^2	PO q6h for 5 doses; start 24 hours after methotrexate
Repeat treatment every 28 days.		
m-BACOD		
Methotrexate	200 mg/m^2	IV on days 8, 15
Leucovorin	10 mg/m^2	PO q6h for 8 doses; start 24 hours after methotrexate
Bleomycin	4 U/m^2	IV on day 1
Adriamycin	45 mg/m^2	IV on day 1
Cyclophosphamide	600 mg/m^2	IV on day 1
Oncovin	1 mg/m^2	IV on day 1 (maximum, 2 mg)
Dexamethasone	6 mg/m^2	PO on days 1-5
Repeat treatment every 21 days.		

[a] Methotrexate given as a 100-mg/m^2 IV bolus, then 300 mg/m^2 IV over 4 hours, followed 24 hours later by leucovorin, 15 mg PO, q6h for 6 doses.