LYMPH NODE PATHOLOGY

selected topics

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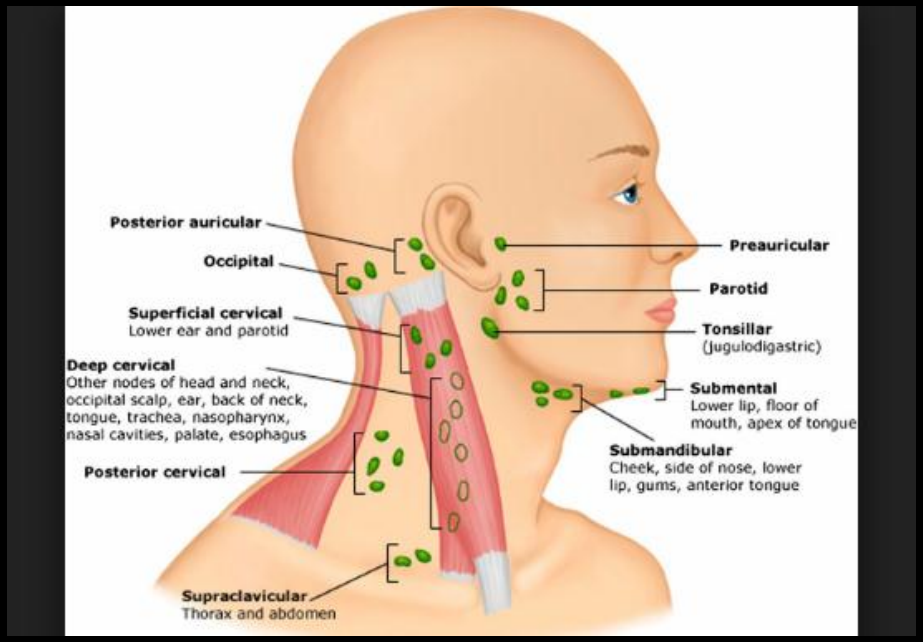
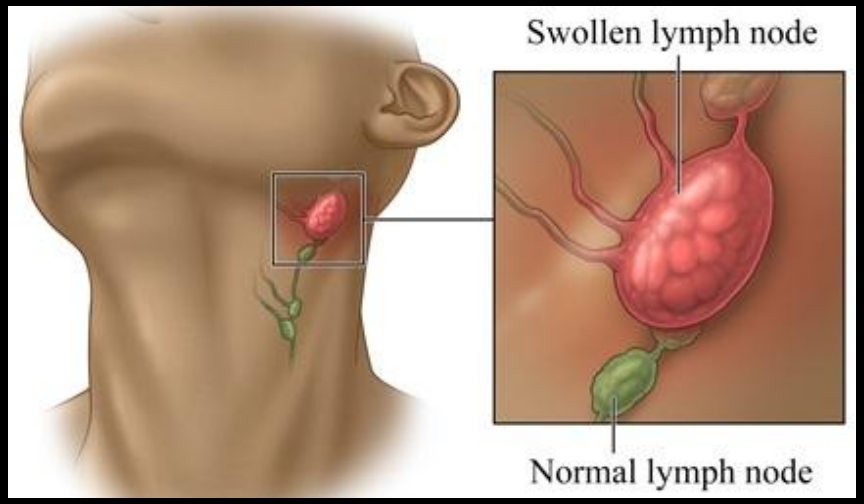
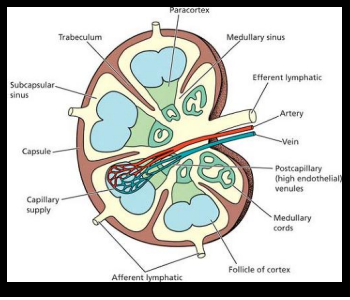
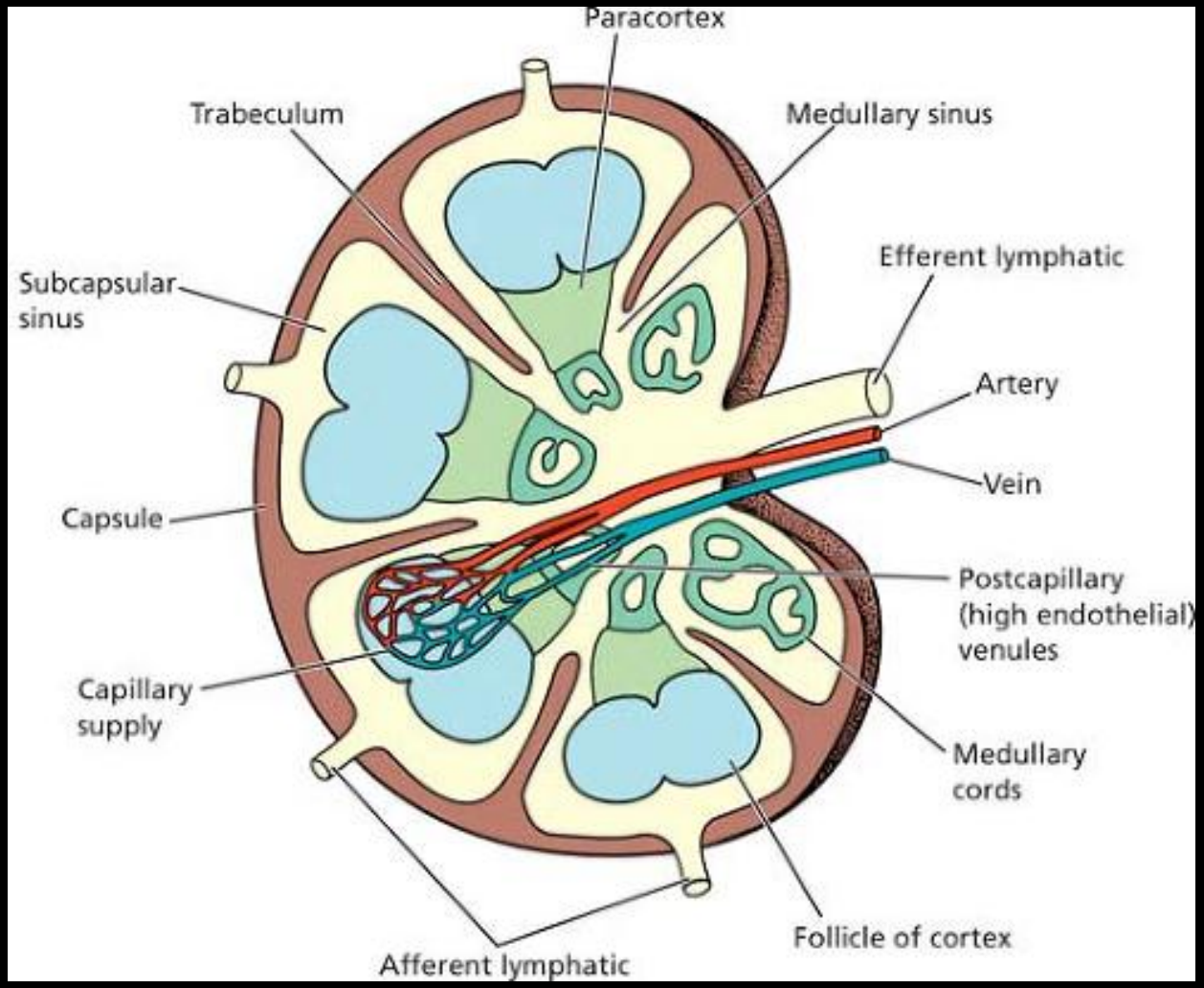


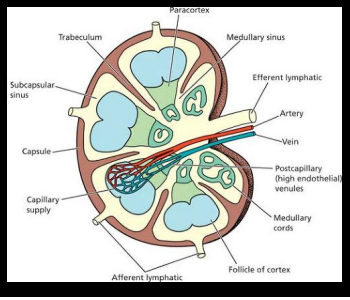




LYMPH NODE - STRUCTURE



- cortex
- paracortex
- medulla
- subcapsular and medullary sinuses



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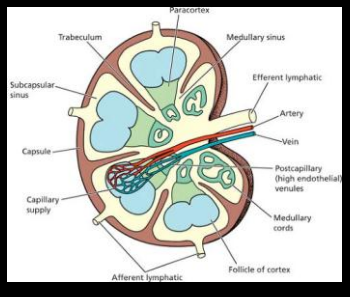
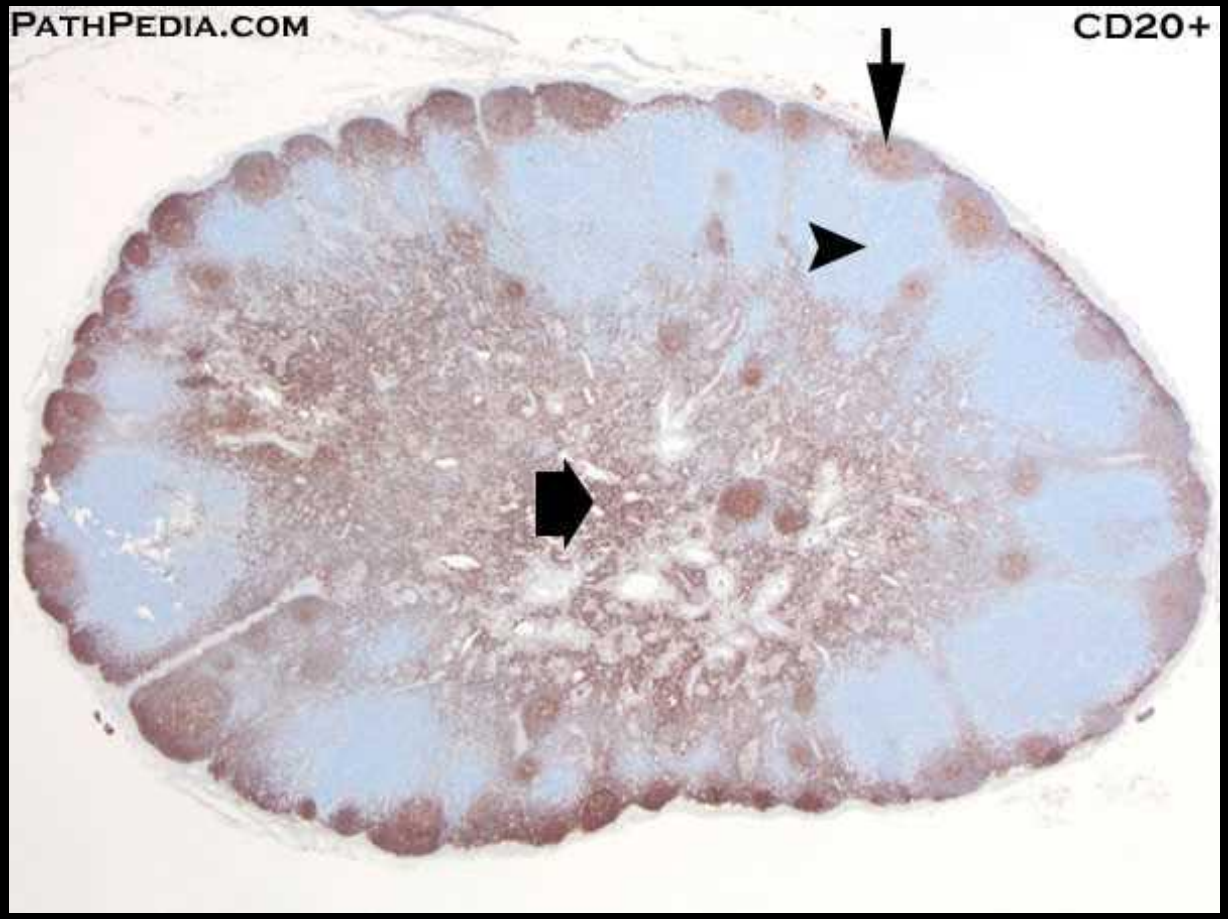
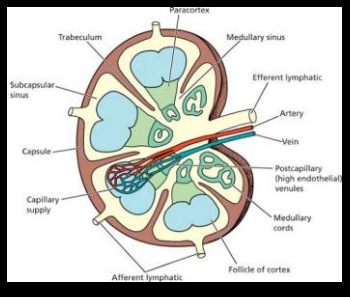


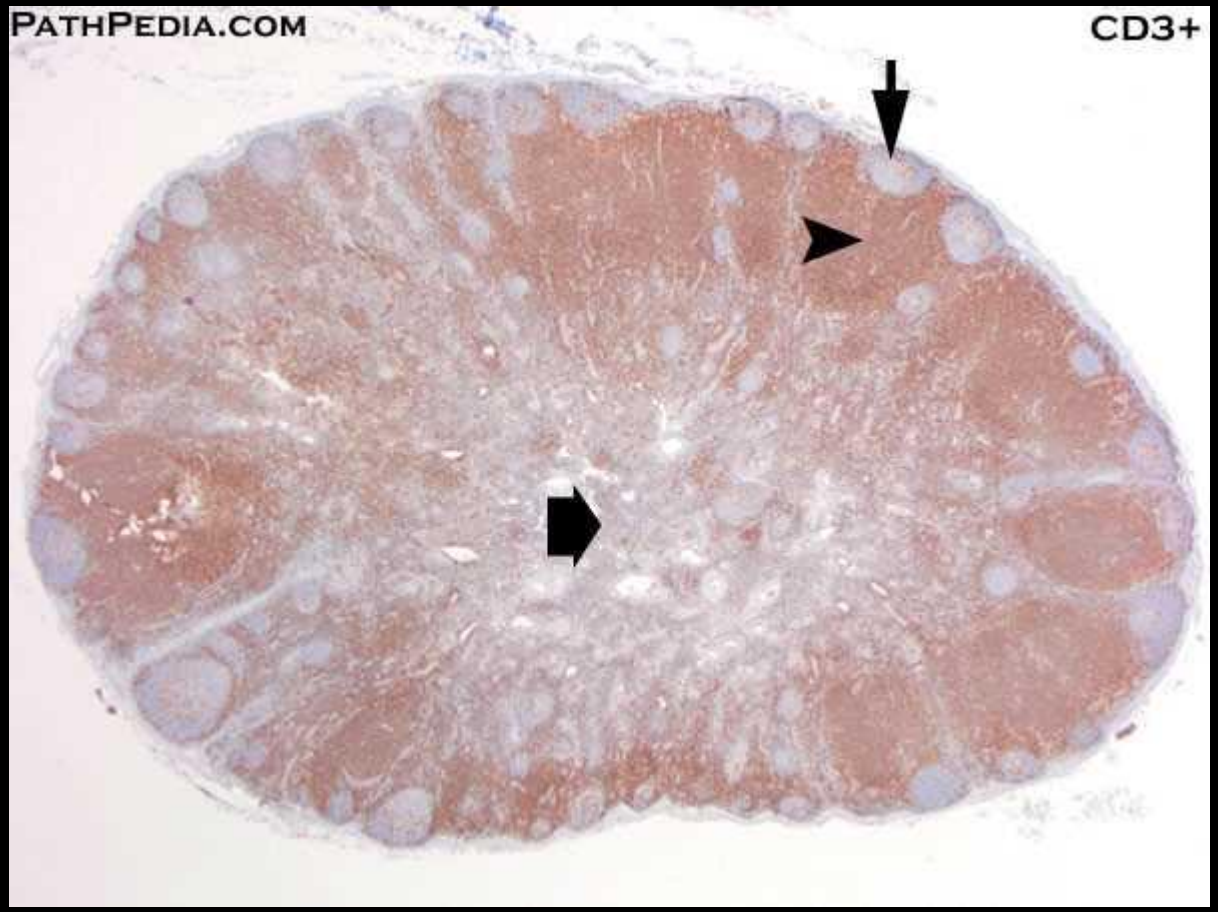
LYMPH NODE – B ZONE



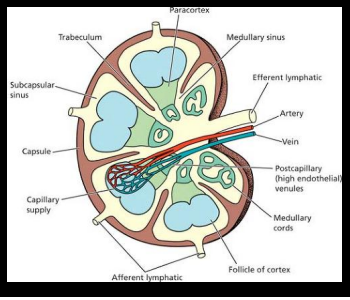
IHC stain: CD20 (marker of B lymphocytes)



LYMPH NODE – T ZONE



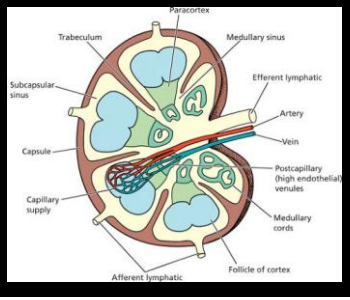
IHC stain: CD3 (marker of T lymphocytes)



LYMPH NODE ENLARGEMENT

LYMPH NODE ENLARGEMENT (LYMPHADENOPATHY)

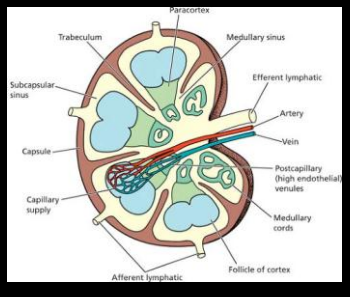
- Non-neoplastic
  - Non-specific
  - Specific
- Neoplastic
  - Primary neoplasms
    - Non-Hodgkin lympnomas
    - Hodgkin lymphoma(s)
  - Metastases



LYMPH NODE ENLARGEMENT - DIAGNOSTICS

Indications for a biopsy?

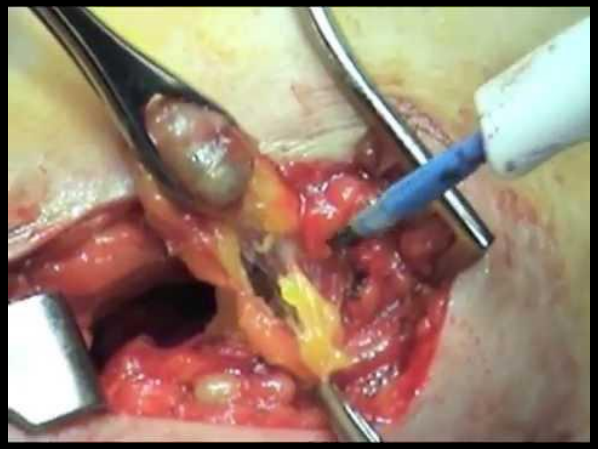
- Significant lymph node enlargement (30-40mm)
- Long-lasting enlargement without known cause
- Indurated/fixed (immobile)/painless lymph node
- Altered echostructure
- Pain after alcohol consumption (Hodgkin lymphoma)
- Isolated lymphadenopathy of selected locations (lower neck, supraclavicular area, abdominal and mediastinal lymph nodes)
- Accompanying general symptoms (fever, night sweeats, unintentional weight loss)
- Worrisome alterations of blood morphology

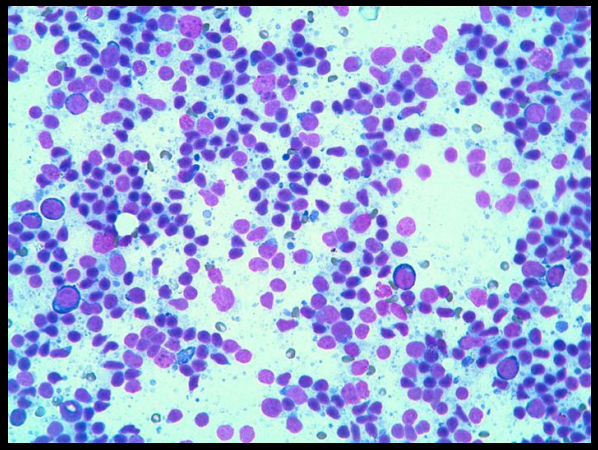


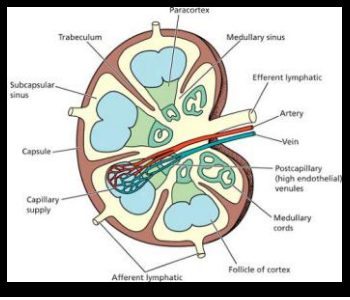
LYMPH NODE ENLARGEMENT - DIAGNOSTICS

Types of biopsy:

- **<u>Excisional</u>**
  - Fine needle
  - Oligobiopsy





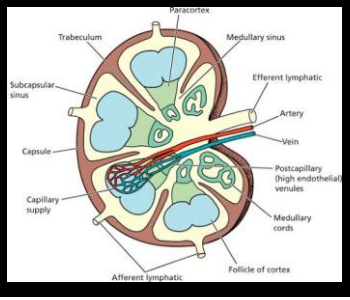


LYMPH NODE ENLARGEMENT - CAUSES

Non-neoplastic, specific:

Toxoplasmosis (*T. gondii*)

- Flu-like symptoms, lemphadenopathy (nuchal area)
- Follicular reaction with phagocytosis of necrotic cell remnants
- Non-necrotizing granulomas of germianl centres
- Extension of subcapsular and medullary sinuses

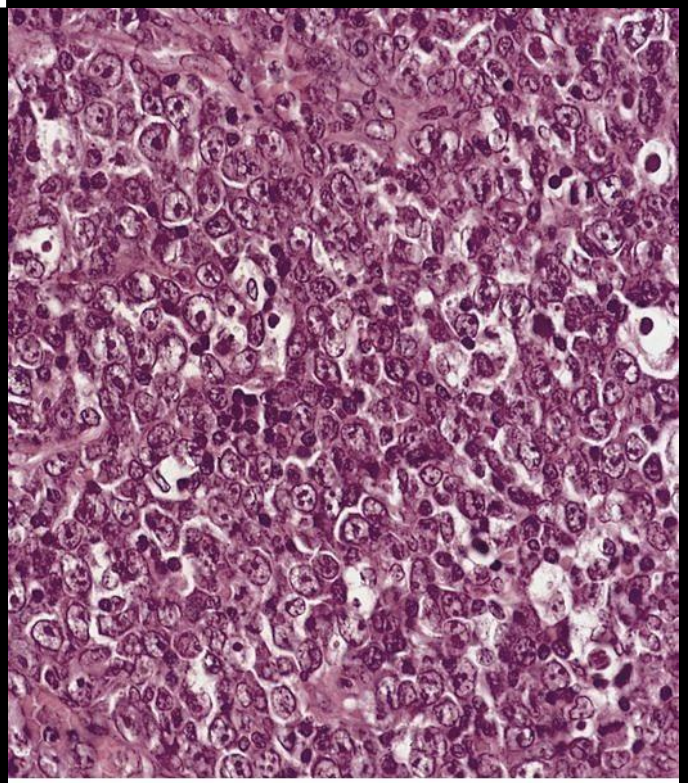


LYMPH NODE ENLARGEMENT - CAUSES

Non-neoplastic, specific:

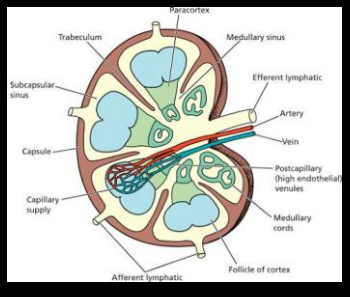
Mononucleosis (*EBV*)

- Lymphadenopathy, splenomegaly, fever, pharyngitis
- Typically diagnosed based on symptoms and blood smear
- Numerous activated large lymphoid cells - immunoblasts (pitfall – expression of CD30, which is also present in Hodgkin lymphoma)



INFECTIOUS MONONUCLEOSIS
INVOLVING LYMPH NODE

There is striking proliferation of immunoblasts which lack significant atypia.

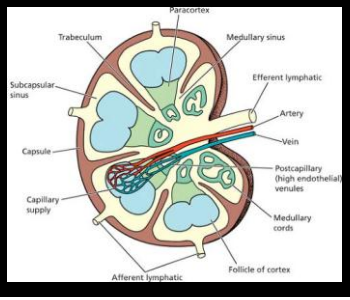


LYMPH NODE ENLARGEMENT - CAUSES

Non-neoplastic, specific:

Suppurative granulomatous lymphadenitis:

- Cat scratch disease(*B. Henslae*)
- Yersiniosis (*Y. enterocolitica*)
- Lymphogranuloma venereum (*Ch. trachomatis*)

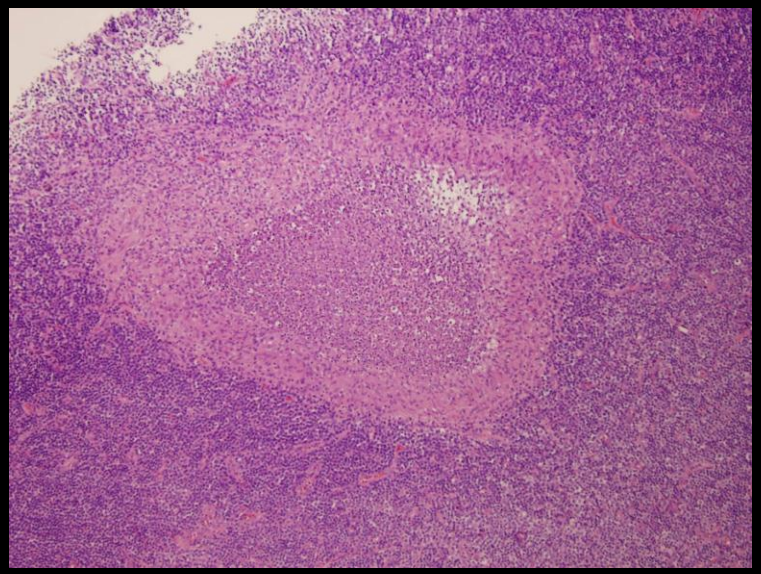


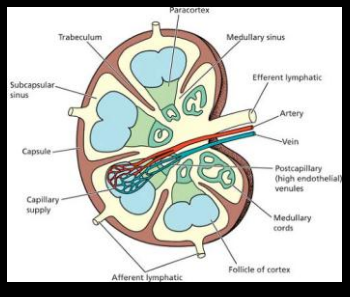
LYMPH NODE ENLARGEMENT - CAUSES

Non-neoplastic, specific:

Suppurative granulomatous lymphadenitis:

- Initially non-characteristic enlargement/activation of lymphatic follicles
- Gradual formation of granulomas with suppuration (accumulation of pus)
- Granulomatous reaction is B cell-dependent (usually other granulomas are related to T cell response)



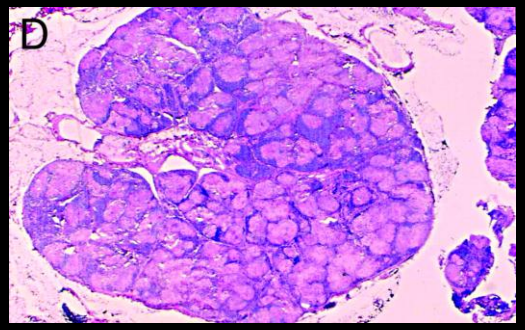


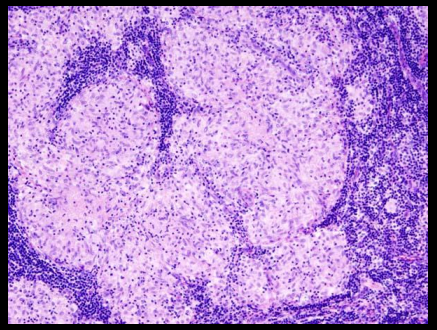
LYMPH NODE ENLARGEMENT - CAUSES

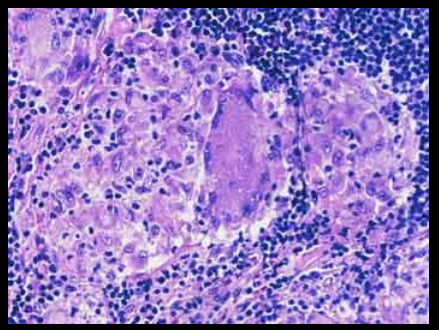
Non-neoplastic, specific:

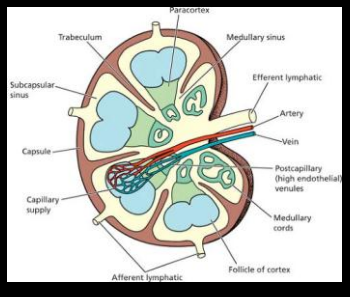
Sarcoidosis

- Systemic disease with unlear etiology affecting most commonly the lungs and lymph nodes
- Fairly characteristic findings are non-necrotizing granulomas that distort/efface the normal architecture of a lymph node
- Langhans giant cells are present
- DDx: **TB!!! -> crucial!!**







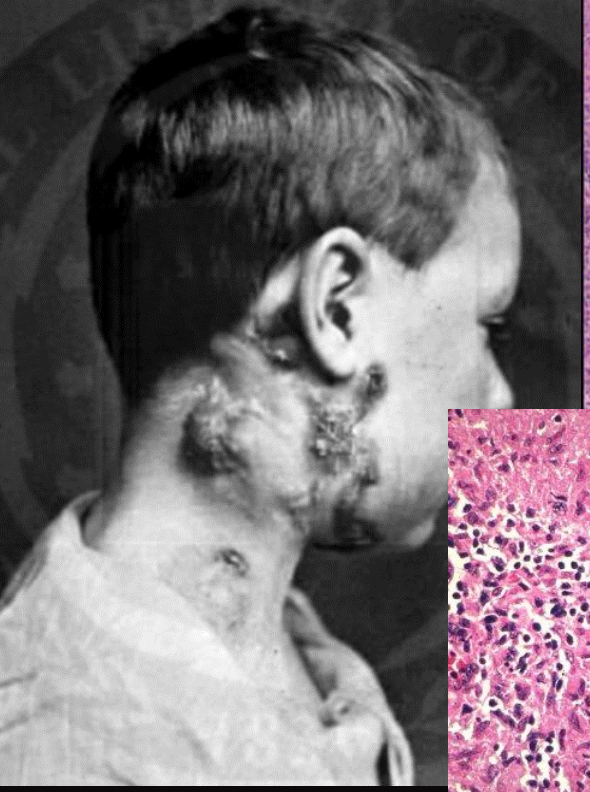
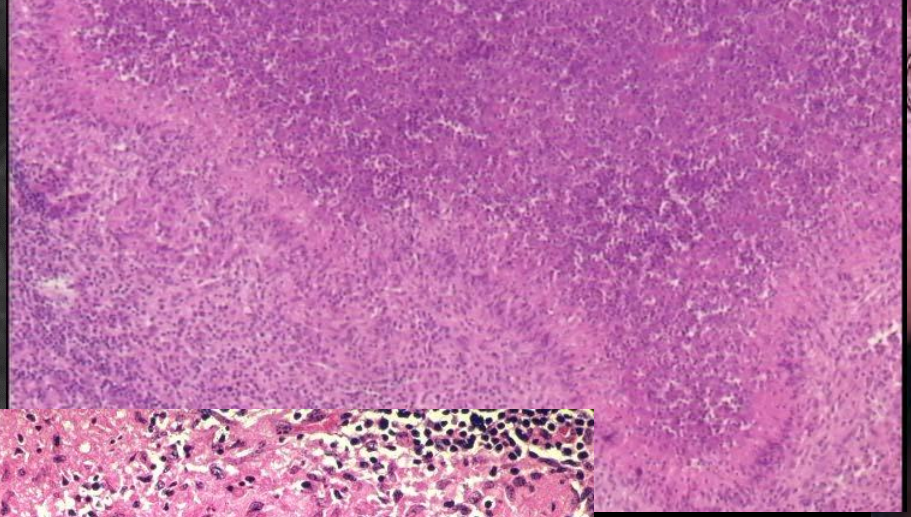
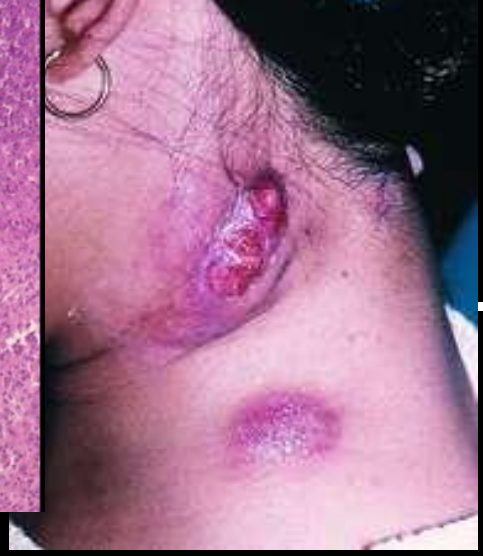
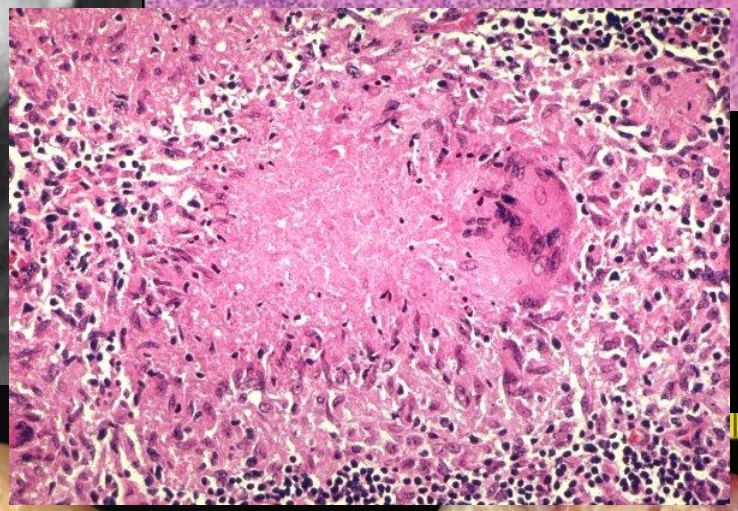
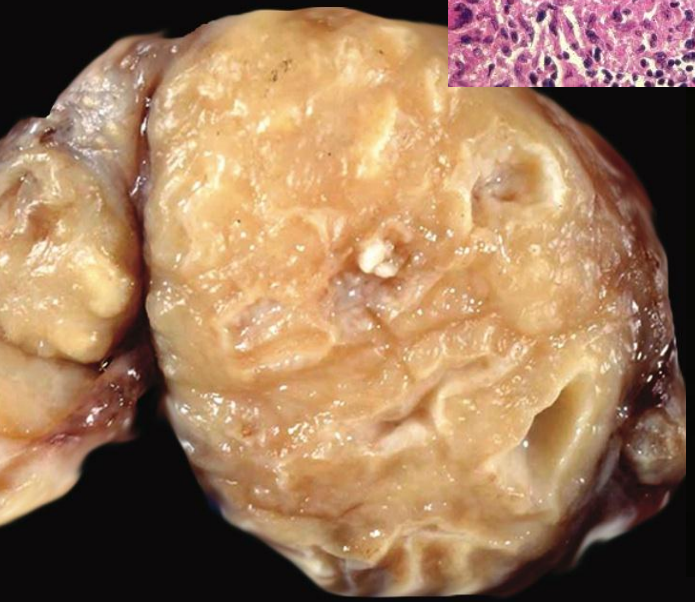
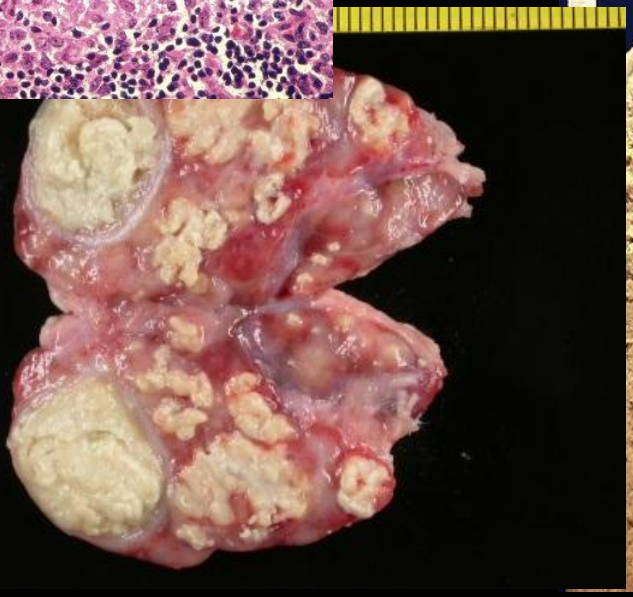


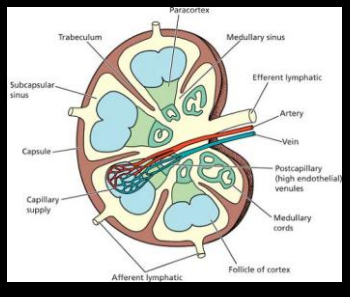
LYMPH NODE ENLARGEMENT - CAUSES

Non-neoplastic, specific:

TB (*M.tuberculosis*)

- Bacterial disease most commonly affecting the lungs, but also the CNS, urogenital tract, skeletal&articular system, skin, lymph nodes
- Formation of granulomas with central necrosis
- Severe, generalized course in immunocompromised patients

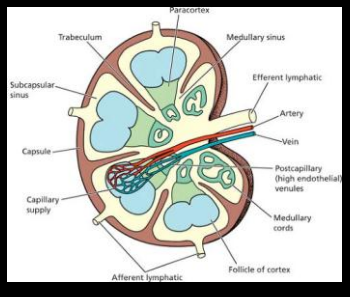







LYMPH NODE ENLARGEMENT - CAUSES

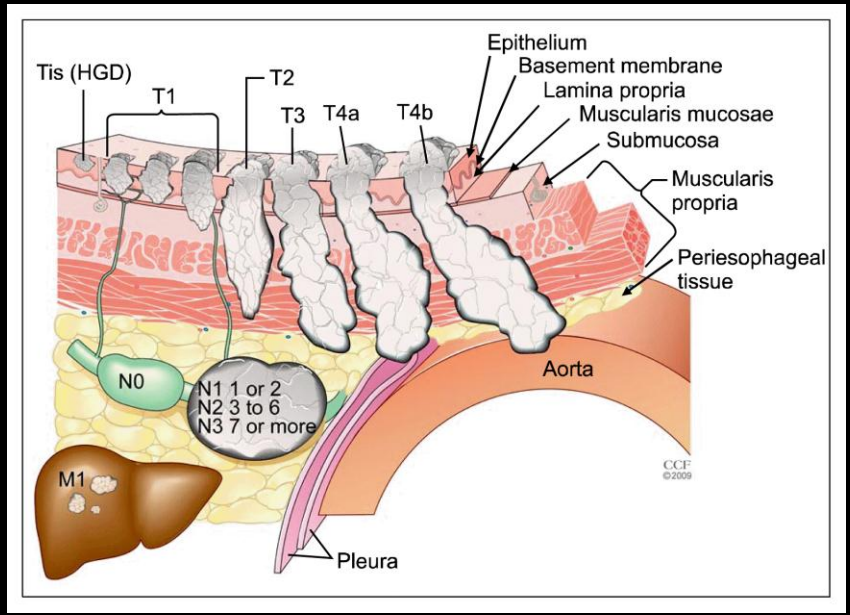
Metastatic tumors

- CARCINOMAS !!!!
- Melanoma
- Sarcomas

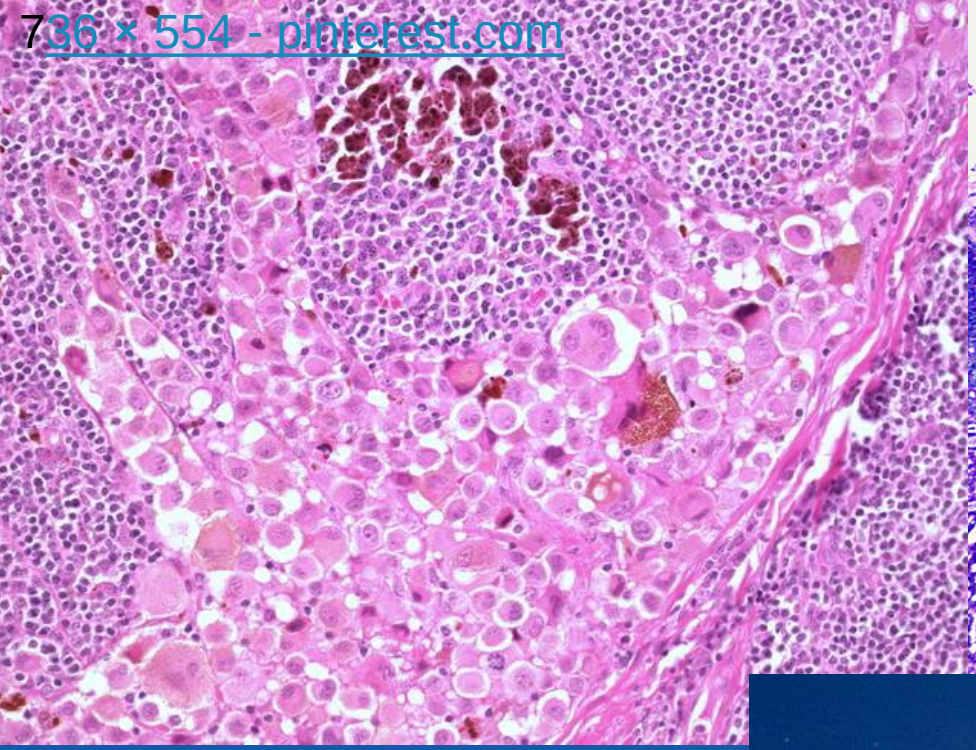


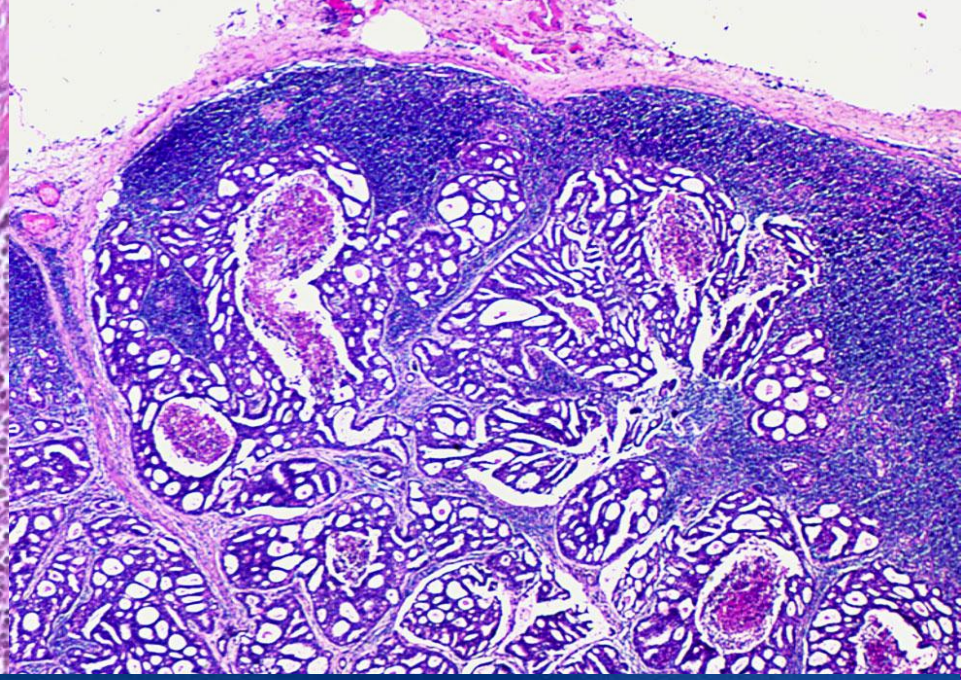
LYMPH NODE ENLARGEMENT - CAUSES

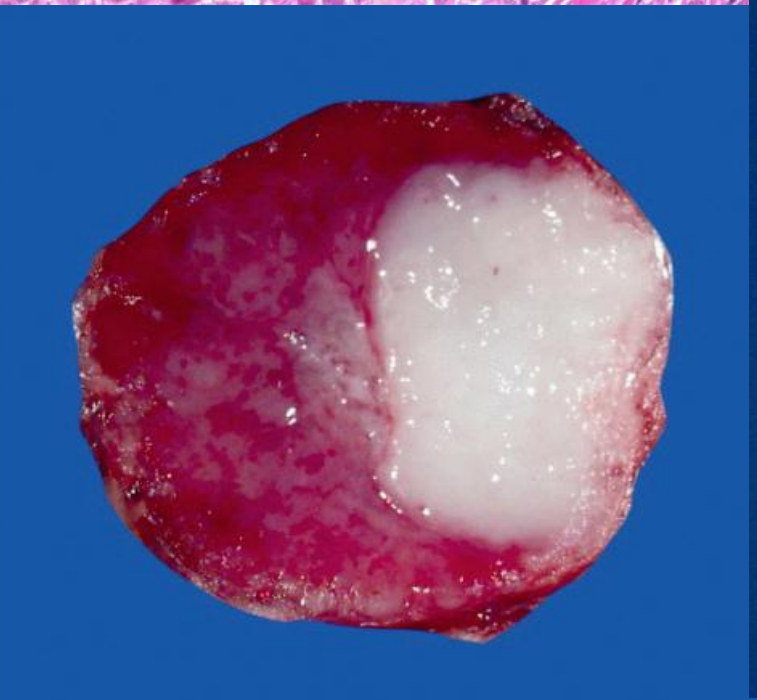
Presence of lymph node metastases is one of key parameters necessary for precise and reliable staging of cancers and for planning the most appropriate therapy

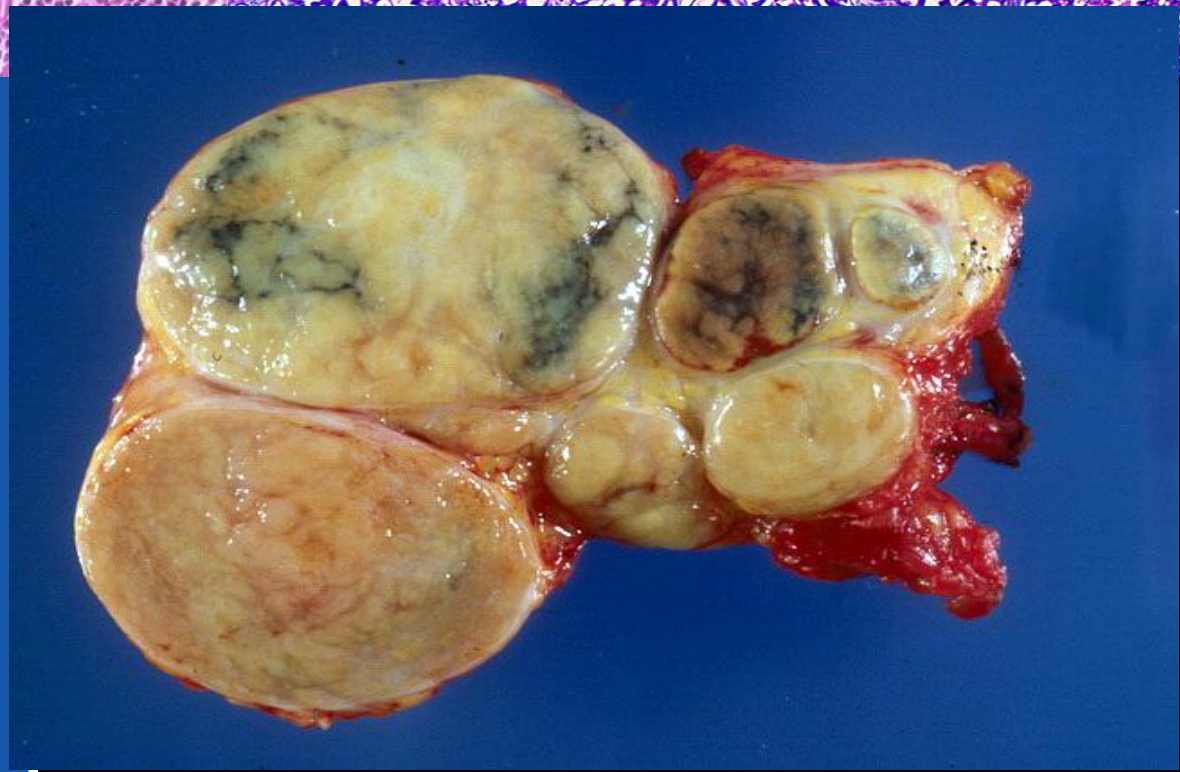


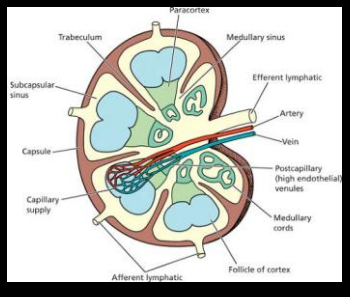
(TNM classification)







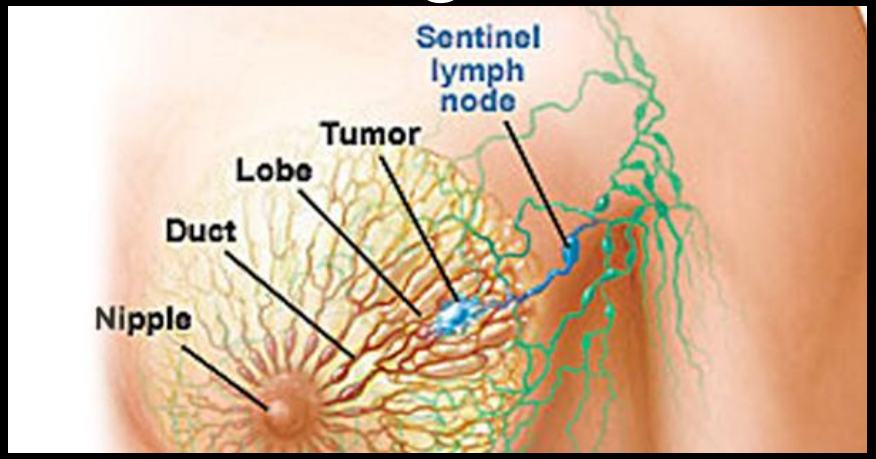


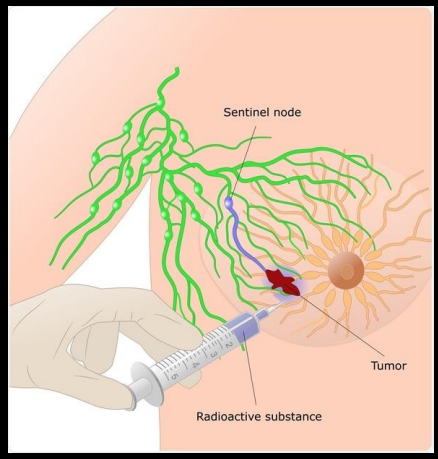


LYMPH NODE ENLARGEMENT - CAUSES

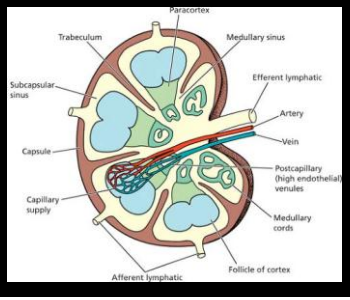
Sentinel lymph node:

The first lymph node (sometimes multiple) draining a location of a tumor





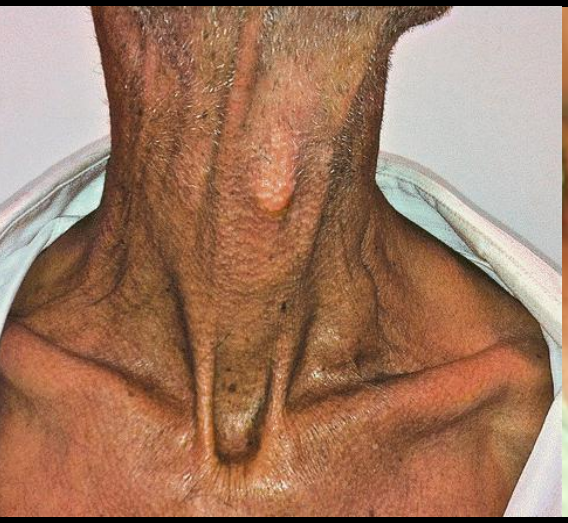
Identification and examination of a sentinel lymph node determines (in selected cases) the necessity of full regional lymphadenectomy

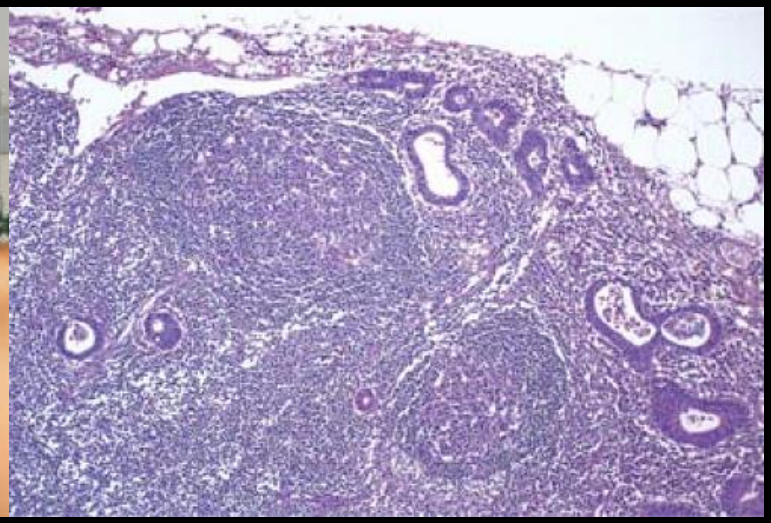


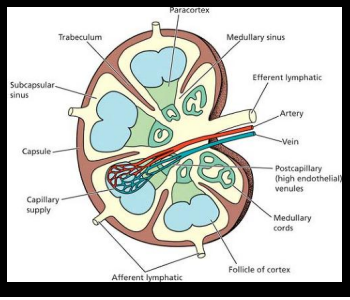
LYMPH NODE ENLARGEMENT - CAUSES

Virchow's lymph node– left supraclavicular lypmh node, typical location of advanced cancers of gastrointestinal tract (stomach, pancreas)

Presence of a metastasis in the Virchow's lymph node (palpable enlargement) is known as a Troisier's sign



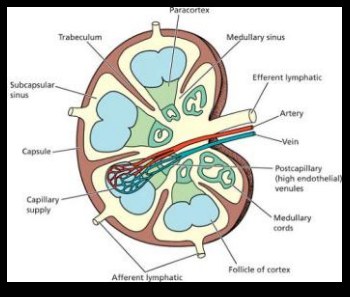




LYMPHOMAS

Lymphomas – large and heterogenous group of **MALIGNANT** neoplasms derived from lymphocytes

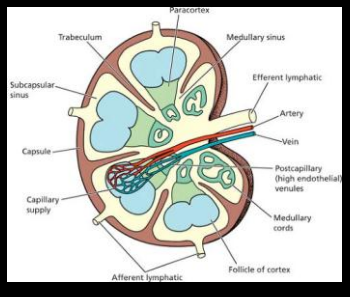
- Etiology is mostly unknown
- Risk factors:
  - Acquired (e.g. methotrexate, HIV) and congenital (e.g. SCID) immunosupression
  - Autoimmune disorders: rheumatoid arthritis, Hashimoto thyroiditis, SLE, Sjoegren's syndrome, coeliac disease
  - Infectious agents: EBV, HHV-8, HTLV1
  - Toxic substances: pesticides, organic solvents
- Diverse clinical course and prognosis
- Therapy is based on chemotherapy



LYMPHOMAS

Division of lymphomas:

- Hodgkin lymphomas (ca. 15%)
  - Classical (4 entities)
  - Non-classical (1 entity)
- Non-Hodgkin lymphomas
  - B cell origin (ca. 80%)
  - T/NK cell (ca. 20%)



LYMPHOMAS

Classical Hodgkin lymphomas:

- NS – nocular sclerosis
- MC – mixed cellularity
- LR – lymphocyte rich
- LD – lymphocyte depleted

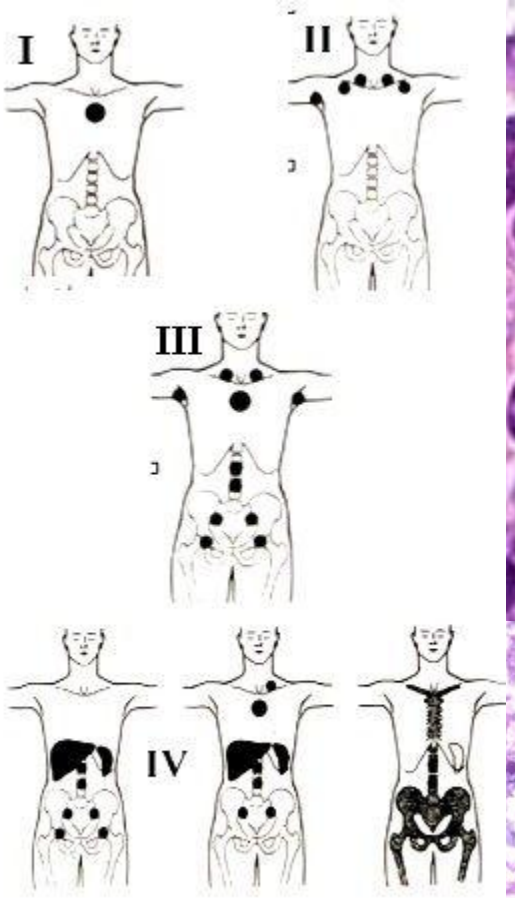
- ❑ Typical non-painful enlargement of lymph nodes of the neck or mediastinum
- ❑ Few neoplastic cells (called Hodgkin cells and Reed-Sternberg /RS/ cells) with numerous reactive non-neoplastic cells
- ❑ Clinical staging based on Ann Arbor classification
- ❑ Good prognosis: 5-year survival - 80-85% patients

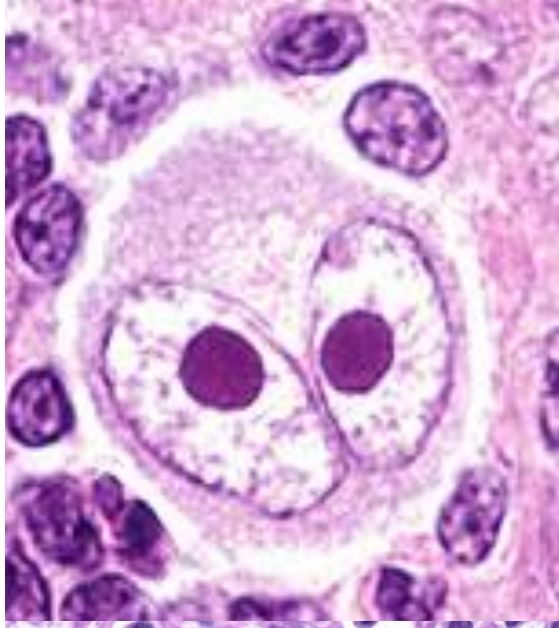
Ann Arbor Staging

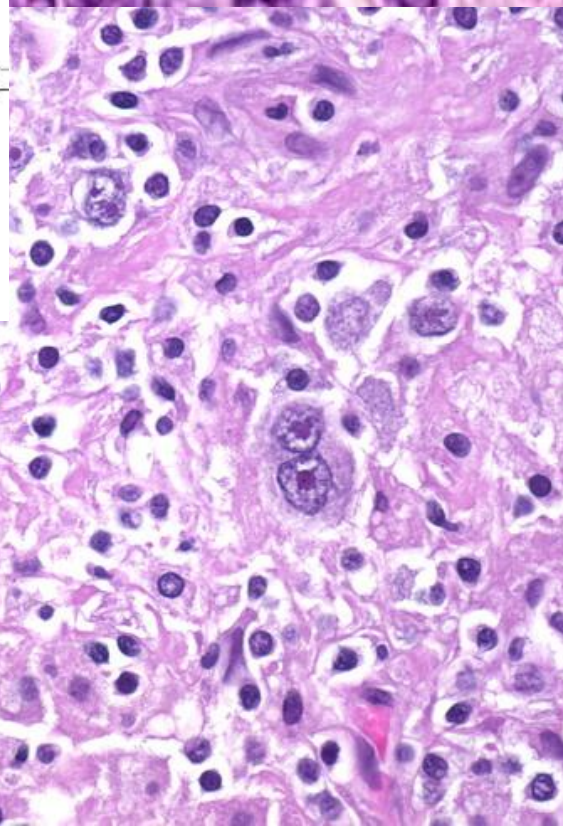
I Single LN region
II One side of diaphragm
III Both sides of diaphragm
IV Disseminated

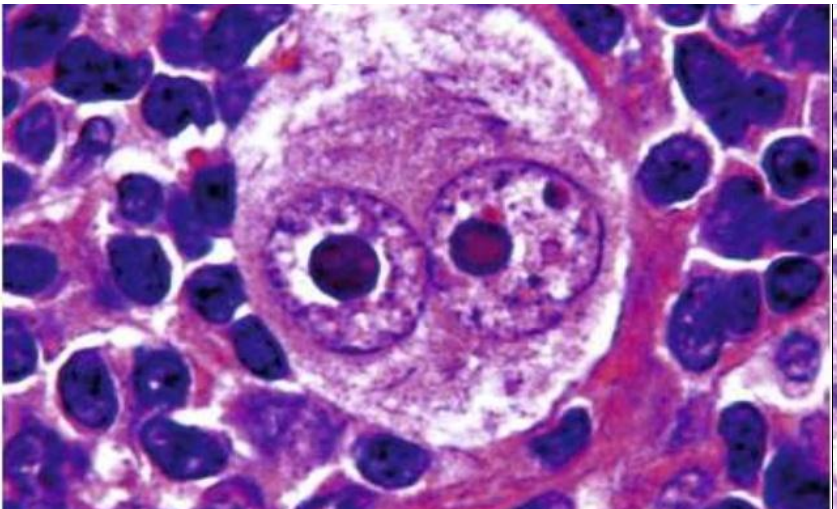
A No systemic symptoms
B Fever, night sweats, weight loss

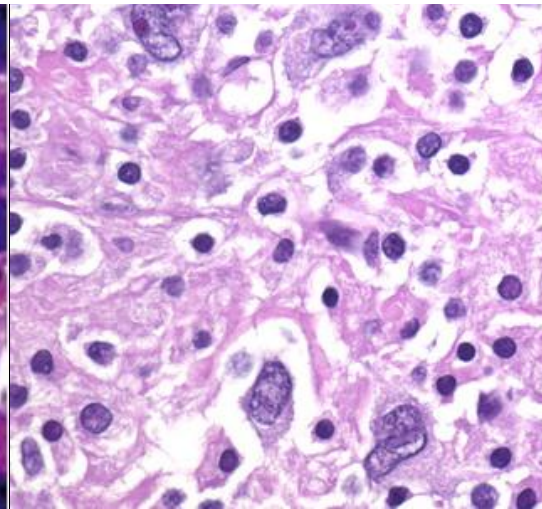
E Extralymphatic site
S Splenic disease

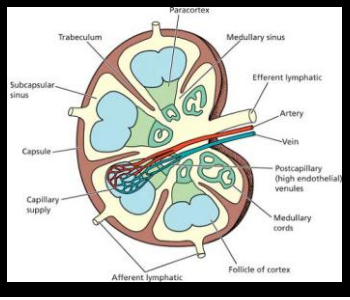








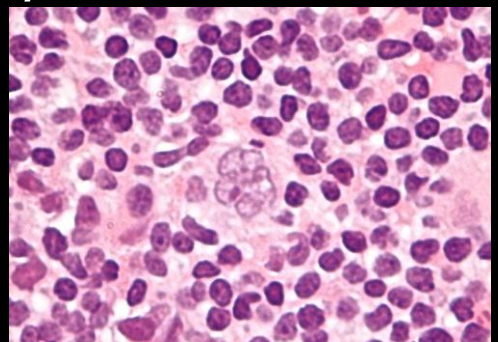


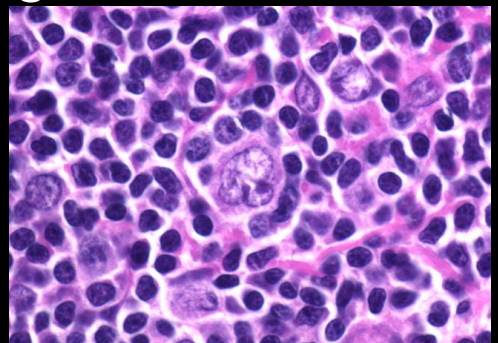


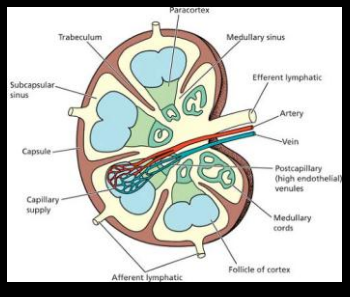
Hodgkin lymphoma, non-classical type:

NLPHL – nodular lymphocyte prediminant Hodgkin lymphoma

- ❑ <5% of all Hodgkin lymphoma cases
- ❑ Distinctive clinical and pathological characteristics
- ❑ Chronic course and very good prognosis in stages I and II
- ❑ *popcorn cells* instead of classical RS/Hodgkin cells

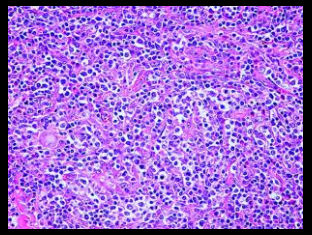
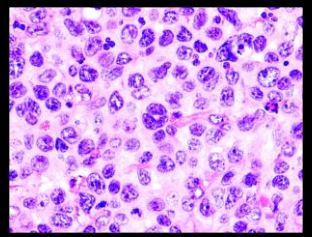
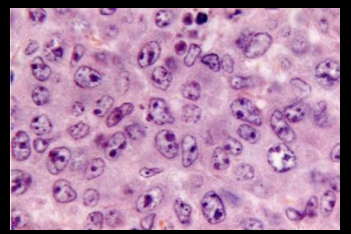
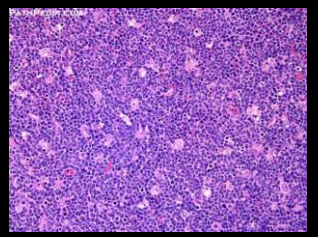


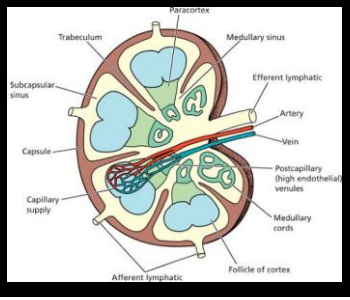




Non-Hodgkin lymphomas (NHL):

- Predominantly B cell type
- Derived from precursor cells or more mature cells
- Heterogenous group of entities with diverse clinical features and variable prognosis
- Diagnosis is based on evaluation of morphology as well as **IMMUNOHISTOCHEMICAL** and molecular features of neoplastic cells



LYMPHOMAS

Most common NHLs:

- Diffuse large B cel lymphoma (DLBCL)
- Follicular lymphoma
- Small lymphocytic lymphoma
- Mantle cel lymphoma
- Marginal zone lymphoma

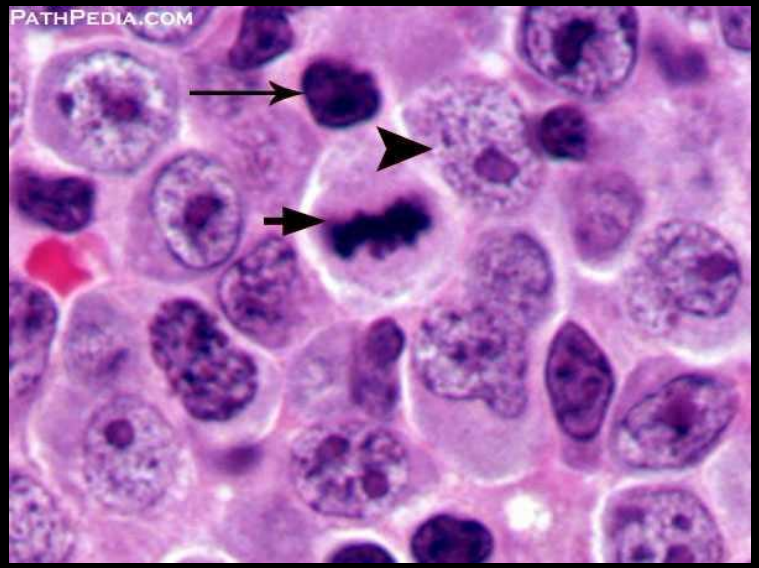


TABLE 2: Immunophenotypic and histochemical markers of B-cell lymphomas/leukemias

	sIg	cIg	CD5	CD10	CD20	CD23	CD43	CD103	Cyclin D1
Follicular	+	–	–	+	+	–(+)	–	–	–
CLL/SLL	dim^{+}	–(+)	+	–	dim^{+}	+	+	–	–
Mantle	+	–	+	–	+	–(+)^	+	–	+
MZL/ MALT	+/+	–(+)/(+)	–/–	–/–	+/+	–/–	–(+)/–(+)	+	–/–
B-cell-PLL*	+	–	–(+)	–	+	+(–)	+	+	–
DLBCL#	+(–)	–(+)	–(+)	–(+)	+	–	–	–	–
HCL	+	–	–	–	+	–	+	–	+(–)
BL/BLL	+	–	–	+	+	–	+	NA	–
LPL	+	+	–	–	+	–	–(+)	–	–

+ = > 90% positive; +(–) = > 50% positive; –(+) = < 50% positive; – = < 10% positive; BL/BLL = Burkitt lymphoma/Burkitt-like lymphoma; cIg = cytoplasmic immunoglobulin; CLL = chronic lymphocytic leukemia; B-cell PLL = B-cell prolymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; HCL = hairy cell leukemia; LPL = lymphoplasmacytic lymphoma; MZL/MALT = splenic marginal zone/mucosa-associated lymphoid tissue; sIg = surface immunoglobulin; SLL = small lymphocytic leukemia

* = A T-cell variant is present in approximately 20% to 30% of PLL cases.

= A T-cell histiocyte-rich B-cell lymphoma variant is present in approximately 1% to 3% of DLBCL cases.

^ = 20% to 25% of cases are CD23+ by flow cytometric immunophenotyping; testing for *bcl-1* is essential.

TABLE 3: Immunophenotypic and histochemical markers of T-cell lymphomas/leukemias

Histology	CD3	CD5	CD7	CD4	CD8	CD30	NK16/56	Cytotoxic granules	TCR
T-PLL	+	–	+	+(–)	–(+)	–	–	–	α/β
T-LGL disease*	+	–	+	–	+	–	+/–	+	α/β >> γ/δ
Mycosis fungoides	+	+	+	+	–(+)	–(+)	–	–	α/β
Cutaneous ALCL	+	+(–)	+(–)	+(–)	(–)	++	–(+)/–(+)	+/–	α/β
Primary systemic ALCL^	+(–)	+(–)	+(–)	–(+)	–(+)	++	–	–	α/β
Peripheral T-cell lymphoma, unspecified	+(–)	+(–)	–(+)	+(–)	–(+)	–(+)	–(+)/–(+)	–(+)	α/β > γ/δ
Subcutaneous panniculitis-like T-cell	+	+	+	–(+)	+(–)	–(+)	–/–(+)	+	γ/δ >> α/β
Hepatosplenic T-cell lymphoma	+	–	+	–	–	–	+/+(–)	+	γ/δ >> α/β
Angioimmunoblastic T-cell lymphoma#	+	+	–	+(–)	–(+)	–	–	–	α/β′
Extranodal NK/T-cell lymphoma	S –, C +	–	–(+)	–(+)	–	–	–/+	+	–
Enteropathy-associated T-cell lymphoma	+	+	+	–(+)	+(–)	+(–)	–	+	α/β >> γ/δ
Adult T-cell leukemia/lymphoma§	+	+	–	+(–)	–(+)	+(–)	–	–	α/β

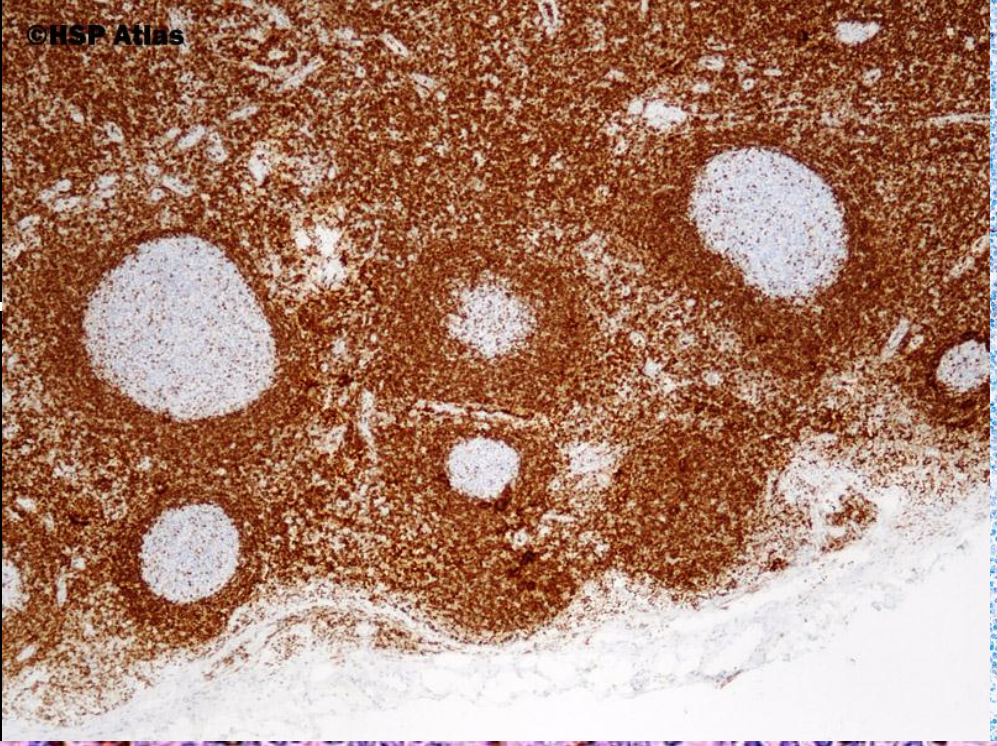
+ = > 90% positive; +(–) = > 50% positive; –(+) = < 50% positive; – = < 10% positive; ALCL = anaplastic large cell lymphoma; C = cytoplasmic; LGL = large granular lymphoproliferative; NK = natural killer; PLL = prolymphocytic leukemia; S = surface; TCR = T-cell–rearranged (molecular)

* Approximately 15% to 20% of LGL cases arise from a NK lineage; they are typically CD56+ and CD16-negative.

^ The anaplastic lymphoma kinase (ALK) protein is expressed in 50% to 60% of cases.

Expanded follicular dendritic cell clusters (CD21+) are present around proliferated venules; Epstein-Barr virus (EBV) genomes are detected in most cases (eg, EBER) and may be present in either T or B cells; in addition, TCR may be negative or oligoclonal in 20% to 25% of cases, whereas B-cell immunoglobulin may be rearranged in 10% of cases.

§ Adult T-cell leukemia/lymphoma cases are always associated with the presence of HTLV-I; further, CD25 is expressed in the majority of cases.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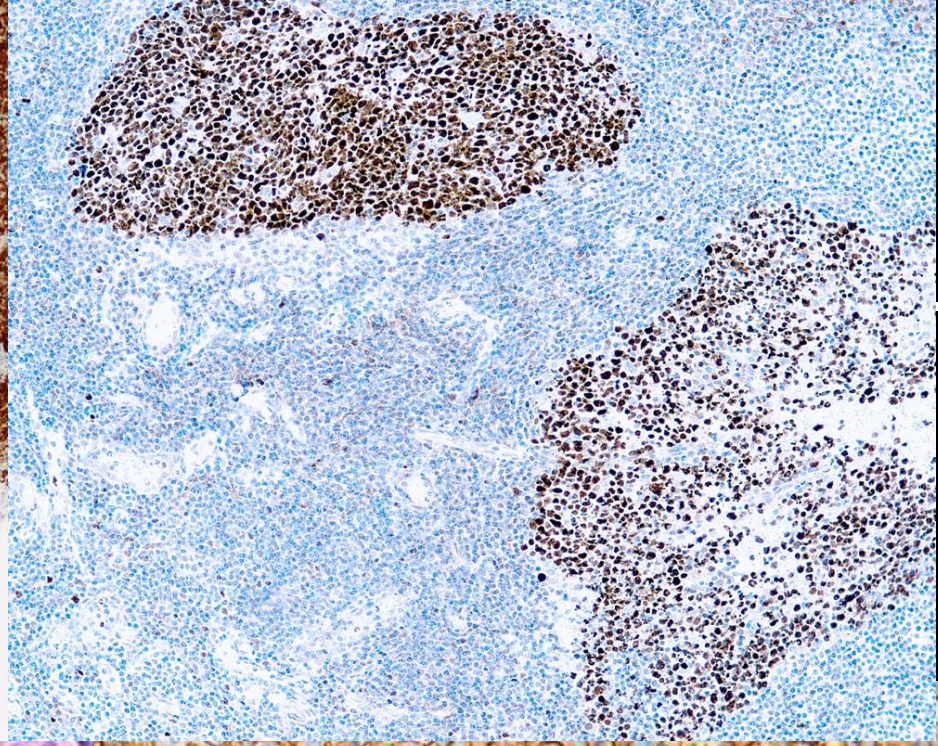
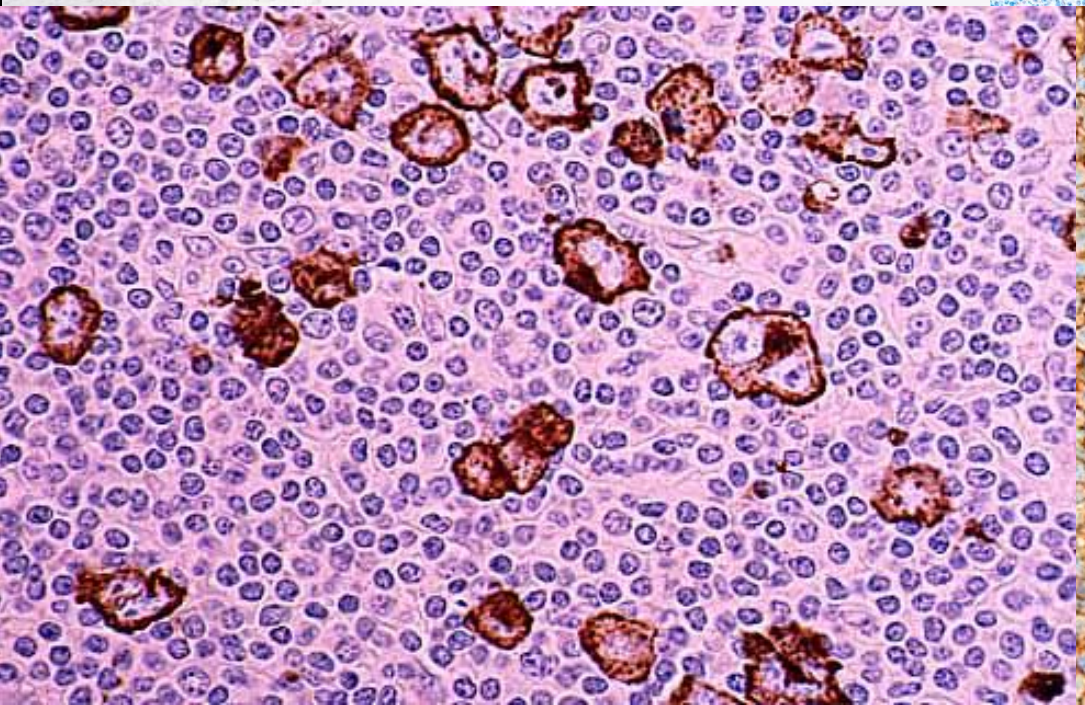
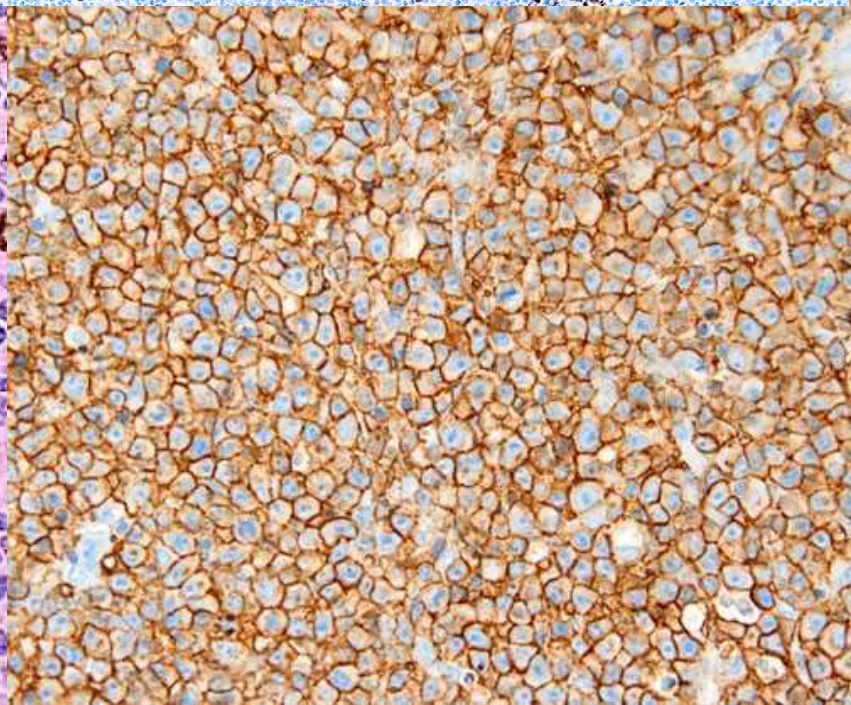






HEMATOPOIETIC SYSTEM

PATHOLOGY CASES

DukeMedicine

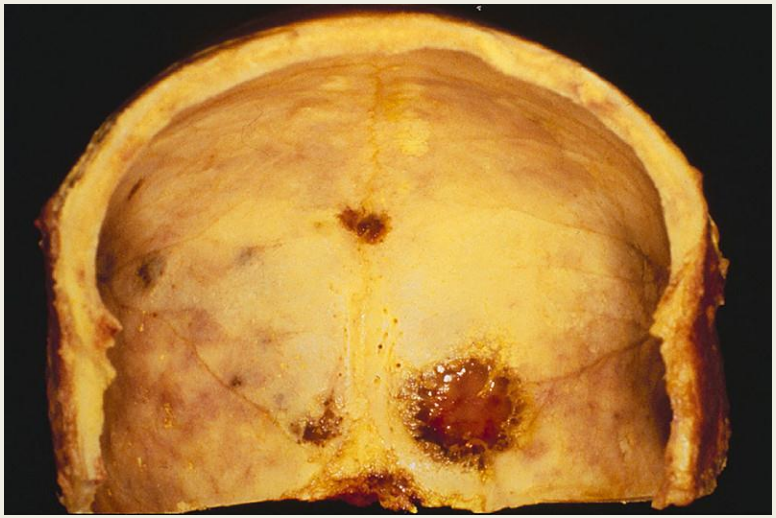
Uniwersytet Medyczny
im. Piastów Śląskich we Wrocławiu

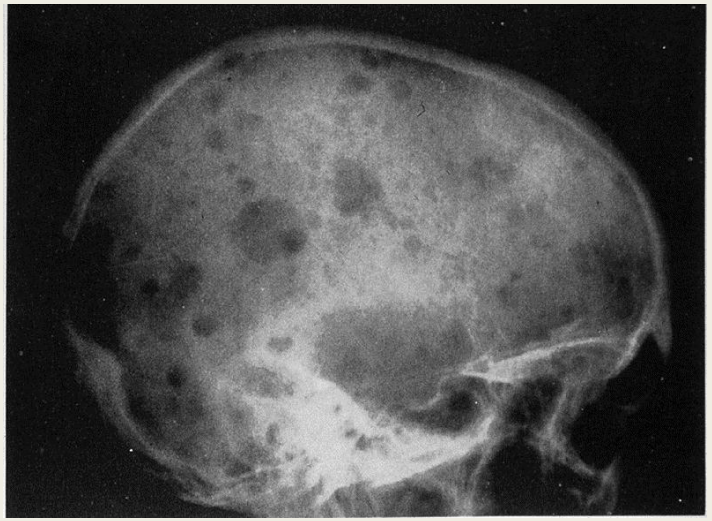
CASE 1

Clinical History:

A 57-year-old man presented to his primary care physician with a 3-month history of back pain and 2-week history of fatigue and weakness. Plain radiograph showed lytic lesions in multiple bones and urinalysis revealed Bence Jones protein. Laboratory analysis showed anemia. A bone marrow biopsy was performed and, based on the diagnosis, chemotherapy and radiation were initiated; however, the patient developed sepsis and died. Radiography, gross and microscopic images are provided.

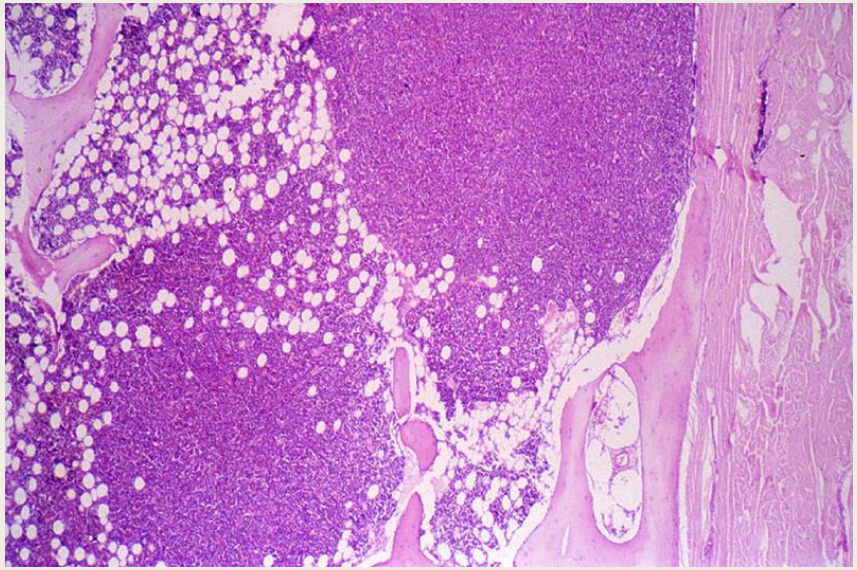
Gross findings



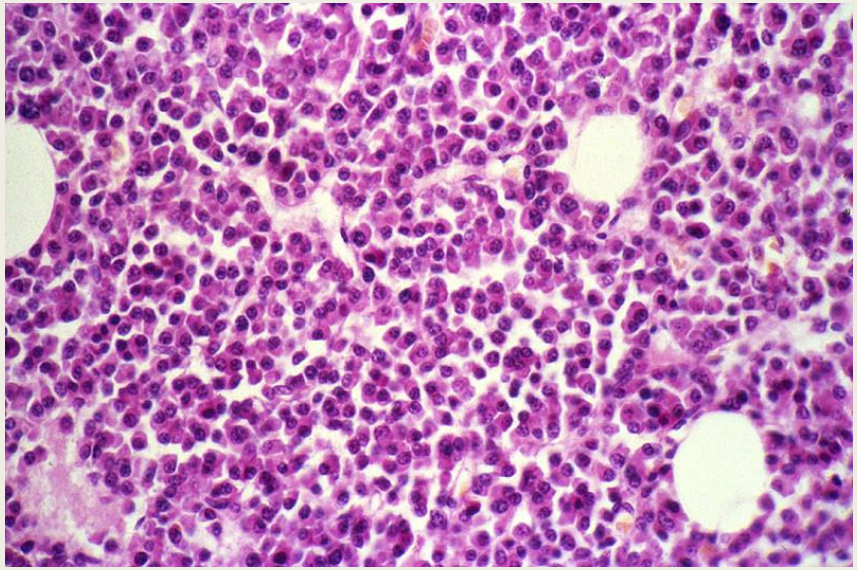


Many of the bones contained poorly delineated, soft gelatinous red tumor masses of various dimensions. Plain film of the skull shows sharply punched out bone lesions.

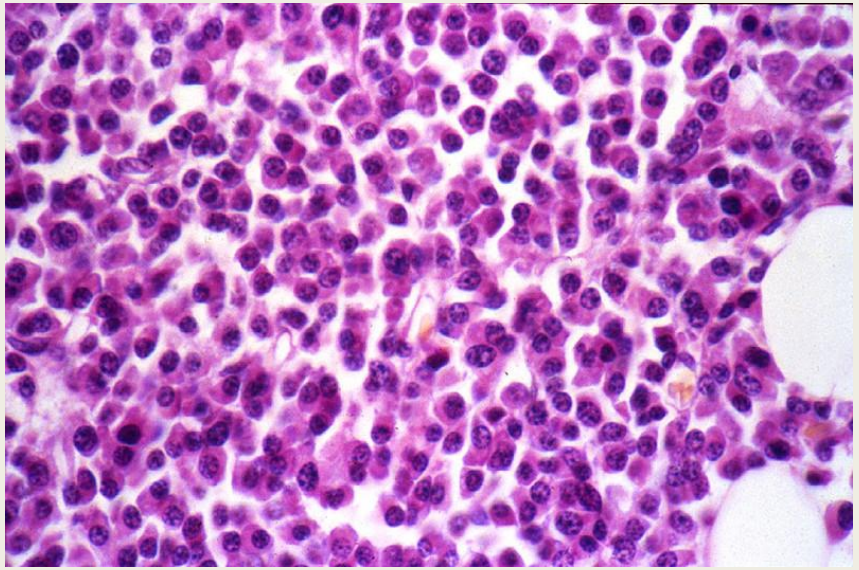
Microscopic findings



Microscopic findings



Microscopic findings



Microscopic findings

aperio.duhs.duke.edu/Pathology_200/0413_Q%20Marrow.svs/view.apml?

The marrow is heavily infiltrated with plasma cells which vary in degree of maturation. Islets of normoblasts are present, but granulocytes and megakaryocytes are markedly decreased. There is considerable loss of trabecular and cortical bone.

Which of the following additional findings is **most likely** in this patient?

- Abundant pulmonary histiocytes
- Amyloidosis
- Multiple cutaneous lesions
- Polycythemia
- Thrombocytosis

Which of the following is true regarding this disease?

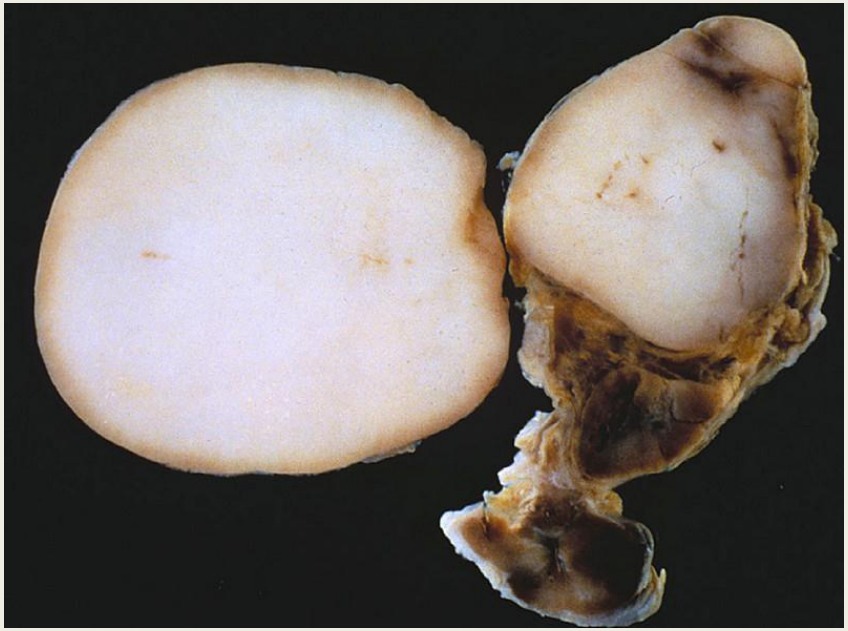
- IgM is the most common serum Ig
- Most patients live >10 years after diagnosis
- Renal insufficiency is rarely the cause of death
- Soft tissue involvement can be seen in advanced disease
- Transformation to diffuse large B cell lymphoma is seen in 25% of patients

CASE 2

Clinical History:

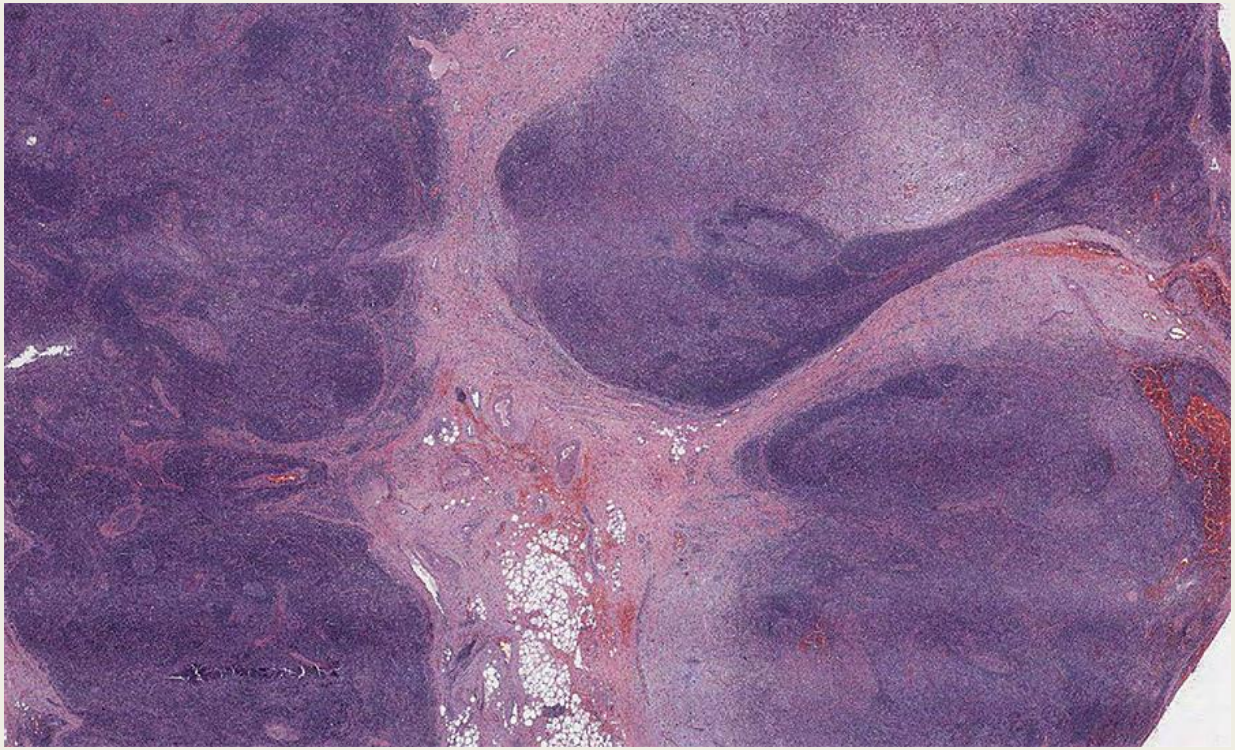
- A 16-year-old boy presented to his pediatrician with a 3 cm mass on right side of his neck. This mass was biopsied. Following diagnosis, a screening CT was performed and revealed a mediastinal mass. Gross and microscopic images of the neck mass biopsy are provided.

Gross findings

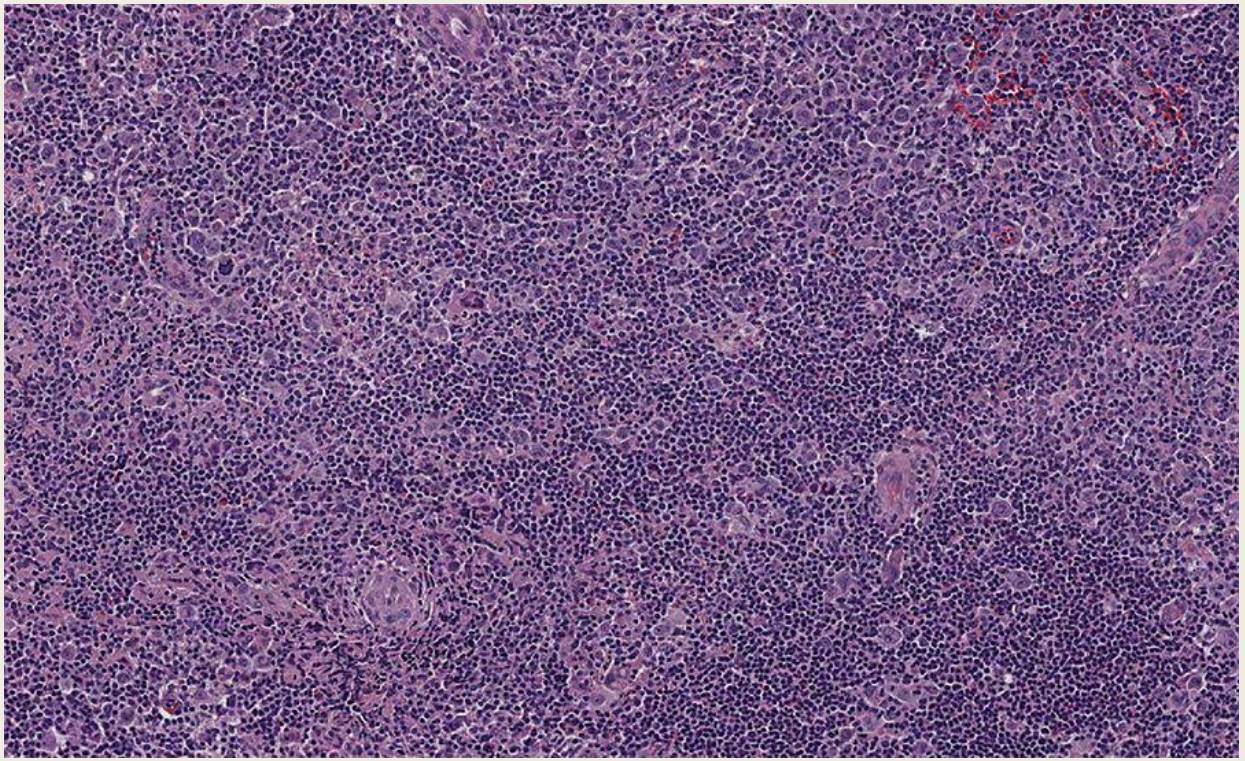


The lymph node was enlarged, and remarkable for fibrous bands separating areas of firm, fleshy material.

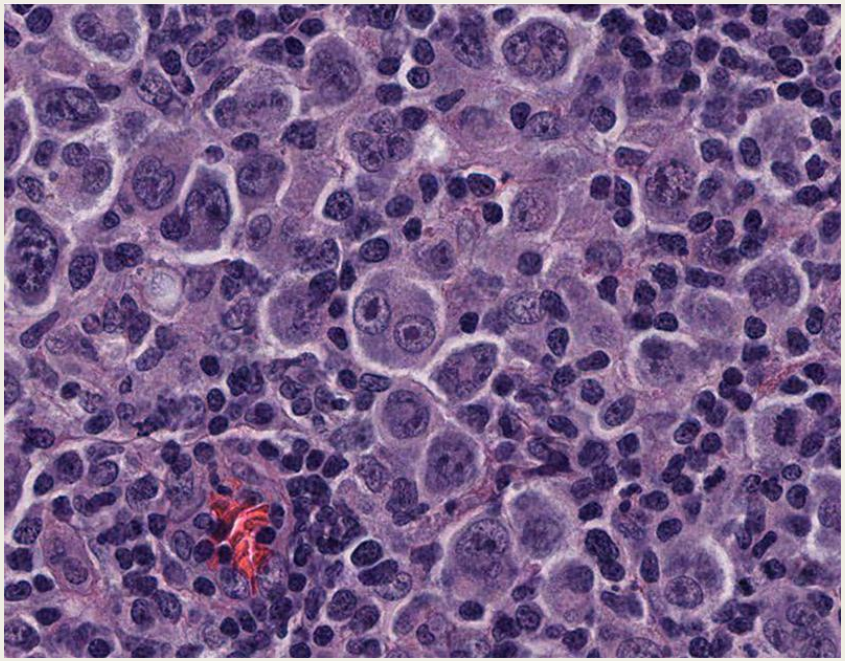
Microscopic findings



Microscopic findings



Microscopic findings



Microscopic findings

http://aperio.duhs.duke.edu/UMichPathology/Heme/UMich_35996nl.svs/view.apml?

The normal lymph node architecture is completely destroyed. In its place are thick bands of collagen, separating islands of lymphoid tissue. In some of these nodules, there is a mixed infiltrate consisting of lymphocytes, eosinophils, some neutrophils and plasma cells, and numerous large cells with highly pleomorphic nuclei. Nuclei are frequently multi lobulated but classic binucleate Reed-Stemberg cells are uncommon. Many cells are so-called "lacunar variants", with nuclei which have artifactually shrunken away from their cytoplasmic borders, leaving a clear space than can often easily be appreciated at low power.

Which of the following is the proposed line of differentiation of the neoplastic cells?

- Germinal center B cells
- Marginal zone B cells
- Mature T cells
- Naïve B cells
- Plasma cells

Which of the following distinguishes this disease from non-Hogdkin lymphomas?

- Extranodal involvement is common
- Frequently involves peripheral lymph nodes
- Mesenteric nodes and Waldeyer ring commonly involved
- Orderly spread to contiguous lymph nodes

Which of the following is **most accurate** regarding this disease?

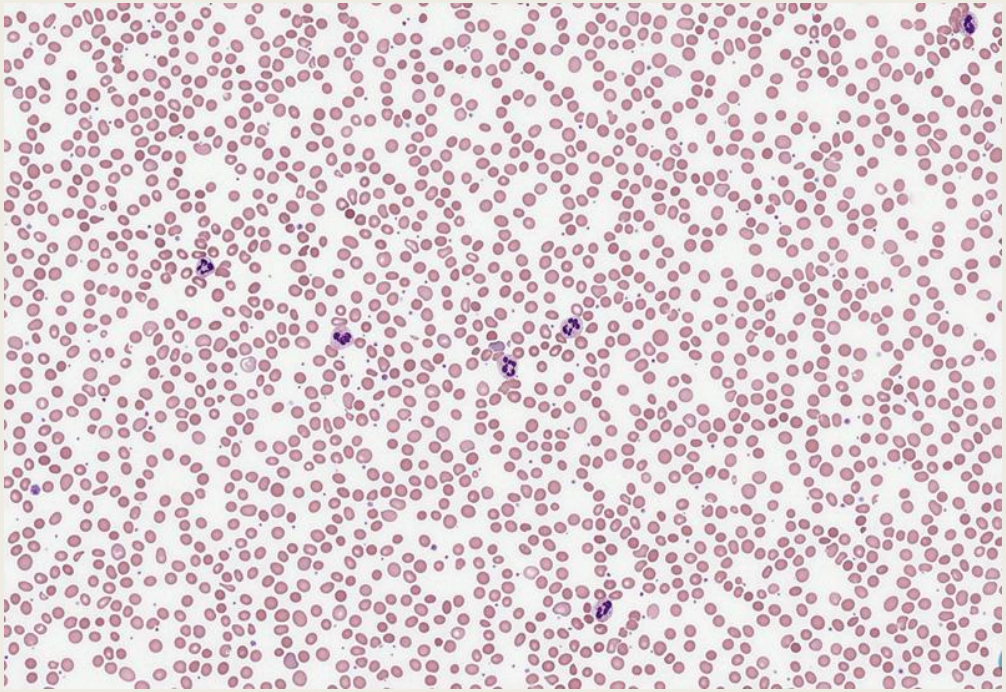
- Epstein-Barr virus infection is common
- It is the least common subtype in this family of diseases
- Lacunar cells are diagnostic
- Males are more commonly affected than females
- Most patients present with Stage III disease or higher

CASE 3

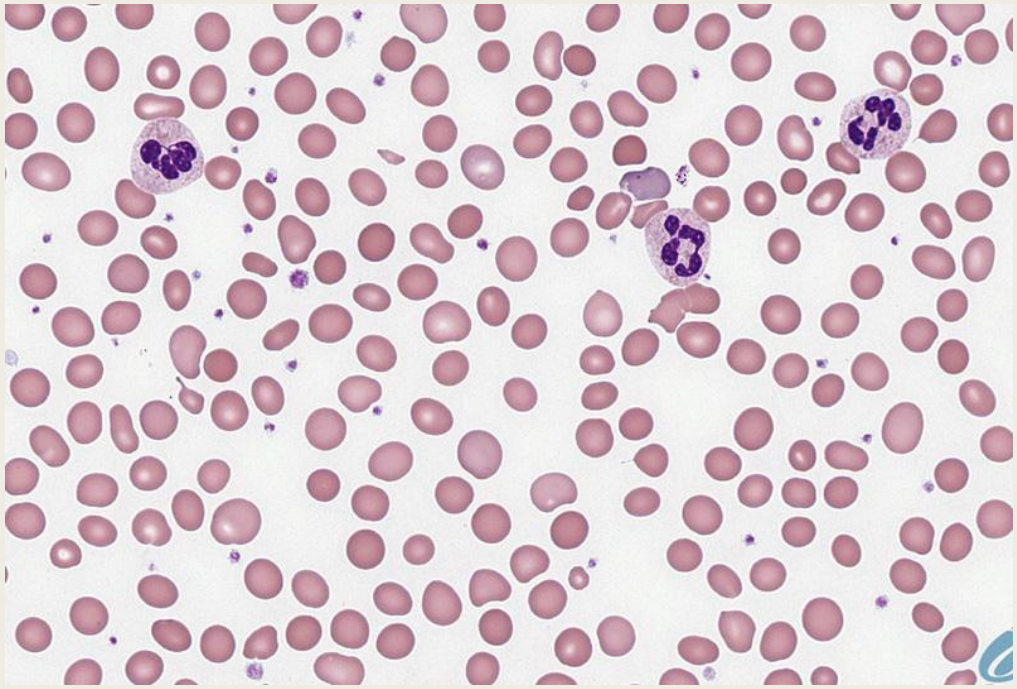
Clinical History:

- A 65-year-old man presented to his primary care physician with a 6-month history of fatigue and weakness and a 2-month history of a burning/tingling sensation in both feet. Physical exam revealed pale mucous membranes and a reddened, smooth tongue. Laboratory analysis showed an increased MCV, a decreased hematocrit and serum antibodies to intrinsic factor. A peripheral smear and a subsequent gastric biopsy are provided for evaluation.

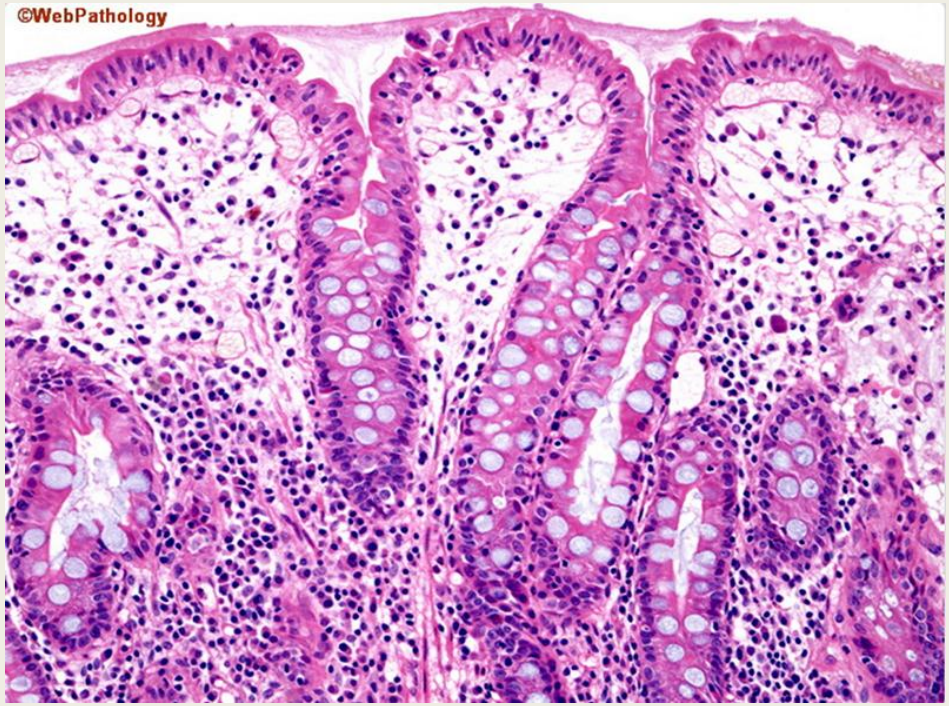
Microscopic findings



Microscopic findings



Microscopic findings



Microscopic findings

http://aperio.duhs.duke.edu/UBC/Heme/2101.svs/view.apml?

The prominent microscopic finding in this peripheral blood smear is the presence of a neutrophil with a nucleus showing at least seven segments. This is called hypersegmentation. The cytoplasm contains appropriate granules. The red blood cells show mild variation in size (anisocytosis). Some large, oval red blood cells are present, and these oval macrocytes show reduced central pallor. Central pallor is not increased in red cells overall. Platelets appear to have normal morphology.

The gastric biopsy shows loss of parietal cells and intestinal metaplasia. There is a deeply seated mixed inflammatory infiltrate consisting of lymphocytes, macrophages and plasma cells.

Which of the following is the **most appropriate** treatment?

- Bone marrow transplant
- High dose folate
- High dose vitamin B12
- Iron supplementation
- Monthly blood transfusions

Which of the following is the **most common** cause of this condition?

- Chronic renal failure
- Infection with parvovirus B19
- Iron deficiency
- Pernicious anemia
- Trauma to red blood cells

This patient has an **increased risk** of developing which of the following?

- Aortic aneurysm
- Cirrhosis of the liver
- Diffuse large B-cell lymphoma
- Gastric carcinoma
- Splenic infarction

Now, based on your backgroud knowledge, knowledge you gained through pathology lectures and lectures as well as additional sources (textbooks, Internet), answer the questions listed on the following slides.

Please send your answers to my University e-mail:
maciej.kaczorowski@umed.wroc.pl

1. What is the cell of origin for multiple myeloma?

A. B lymphocyte
B. T lymphocyte
C. Plasma cell
D. NK cell

2. Which sentence is false?

A. All lymphomas are malignant.
B. Only some of lymphomas are aggressive.
C. Long survival (10 years and more) is possible in cases of some lymphomas.
D. Hodgkin lymhomas are incurable.

3. Give at least one possible disease characterized by granulomatous enlargement of lung hilar lymph nodes.

4. Lymph node biopsy is always the optimal management of lymphadenopathy.

A.No.

B.Yes.