LYMPHADENOPATHY

MUW 2010/2011

B. Schneeweiss

LYMPH NODES REGIONS

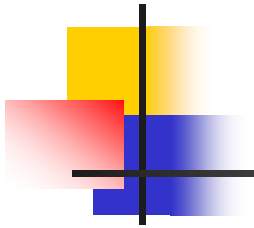
- retro- and preauricular
- nuchal
- submandibular
- scalene nodes
- supra- and infraclavicular
- axillary
- inguinal
- mediastinal
- abdominal

NORMAL LYMPH NODES

- soft
- flat
- submandibular
- < 1 cm
- often found in children and young adults
- in healthy adult occasional found lymph nodes up to 2 cm in diameter

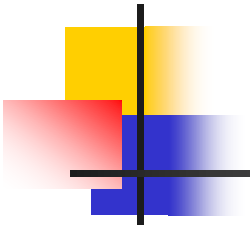
CAUSES OF LYMPHADENOPATHY

- benign increase (immune reaction) of
  - B-lymphocytes
  - T-lymphocytes
  - makrophages
- infiltration by granulocytes or monocytes (infection of the lymph nodes)
- proliferation of malignant cells in the lymphocytes (monoclonal proliferation)
- metastatic
- accumulation of amorphous substances
  - amyloid, lipids



LYMPHADENOPATHY

- infectious diseases
  - viral
  - bacterial
  - fungal
  - chlamydial
  - parasitic
  - rickettsial
- immunologic diseases
- malignant diseases
  - hematologic
  - metastatic
- Lipid storage diseases
- endocrine diseases



CAUSES OF LYMPHADENOPATHY

- other diseases
  - Castleman's disease (giant lymph node hyperplasia)
  - Sarcoidosis
  - dermatopathic lymphadenitis
  - lymphomatoid granulomatosis
  - histioytic necrotising lymphadenitis (Kikuchi's disease)
  - sinus histiocytosis with massive lymphadenopathy (Rosai-Dorfman-disease)
  - mucocutaneous lymph node syndrome (Kawasaki's disease)
  - Histiocytosis X
  - familial mediterranean fever
  - severe hypertriglyceridemia
  - vascular transformation of sinuses
  - inflammatory pseudotumor of lymph node
  - congestive heart failure

CLINICAL ASSESSMENT

Medical history

- B-symptomatic
- frequent infections
- sexual behaviour
- travel abroad
- contact to animals
- drugs
- duration of lymphadenopathy

CLINICAL ASSESSMENT

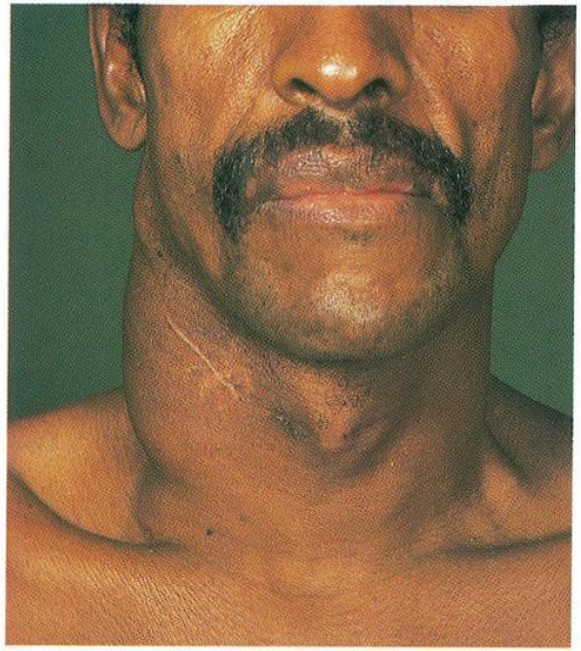
physical examination

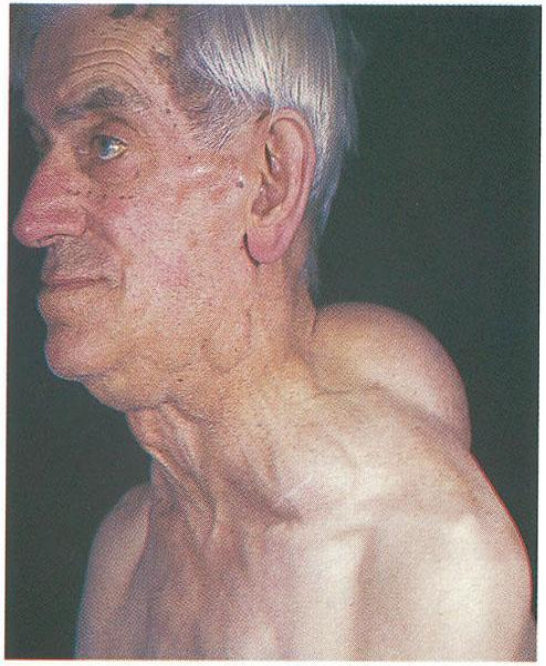
- extent of lymphadenopathy (localized/generalized lymphadenopathy)

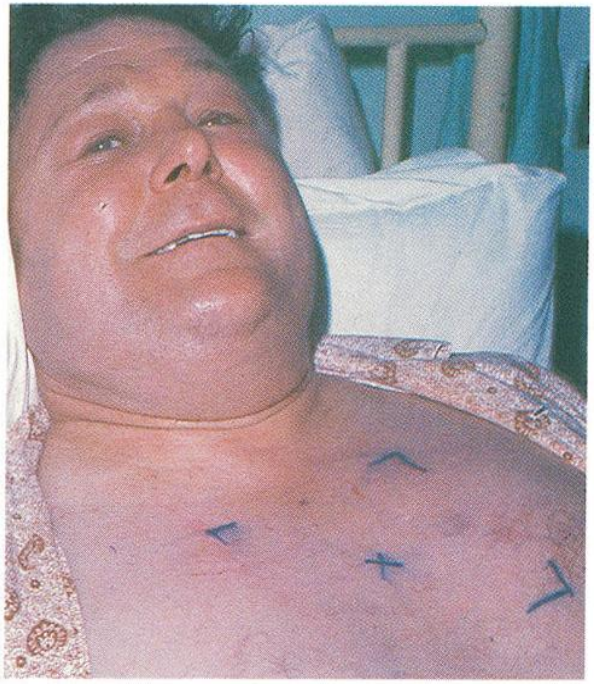
  size of nodes, dexture and tenderness, signs of inflammation

  locoregional inflammation?

- hepato-/splenomegaly







LABORITORY INVESTIGATION

complete blood count

chemistry (LDH, CRP)

molecular biology in NHL

tumormarkers ??

bacterial cultures

histology and cytology

antibody studies (anti-DNA)

angiotensine converting enzyme

LABORITORY INVESTIGATIONS

serologic studies

EBV, CMV, HIV, other viruses, *Toxoplasma gondii, Brucella, Tularemia*

IMAGING TECHNIQUES

ultrasonography of lymph nodes

chest x-rey

ultrasound

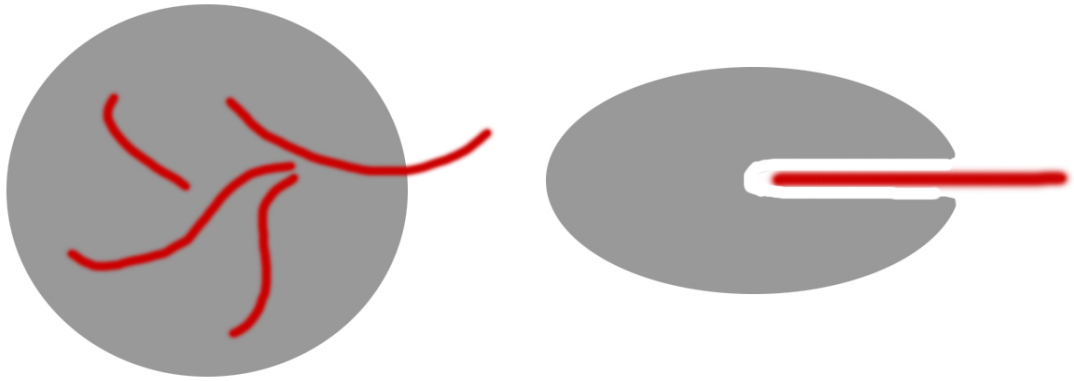
CT

PET

MRI

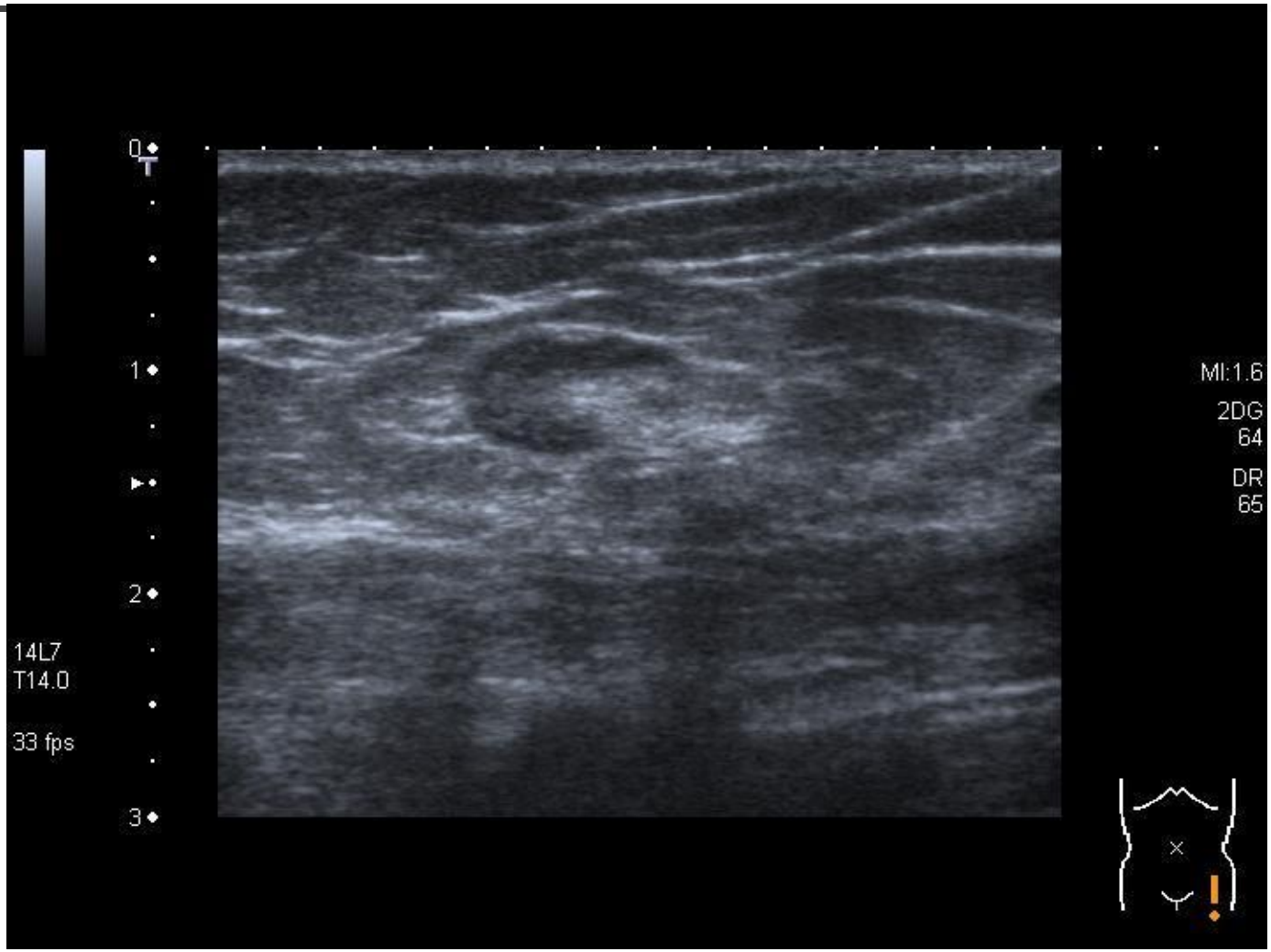
ULTRASONOGRAPHY

High specifity and sensivity to discriminate between benigne and malignant lymph node enlargements.

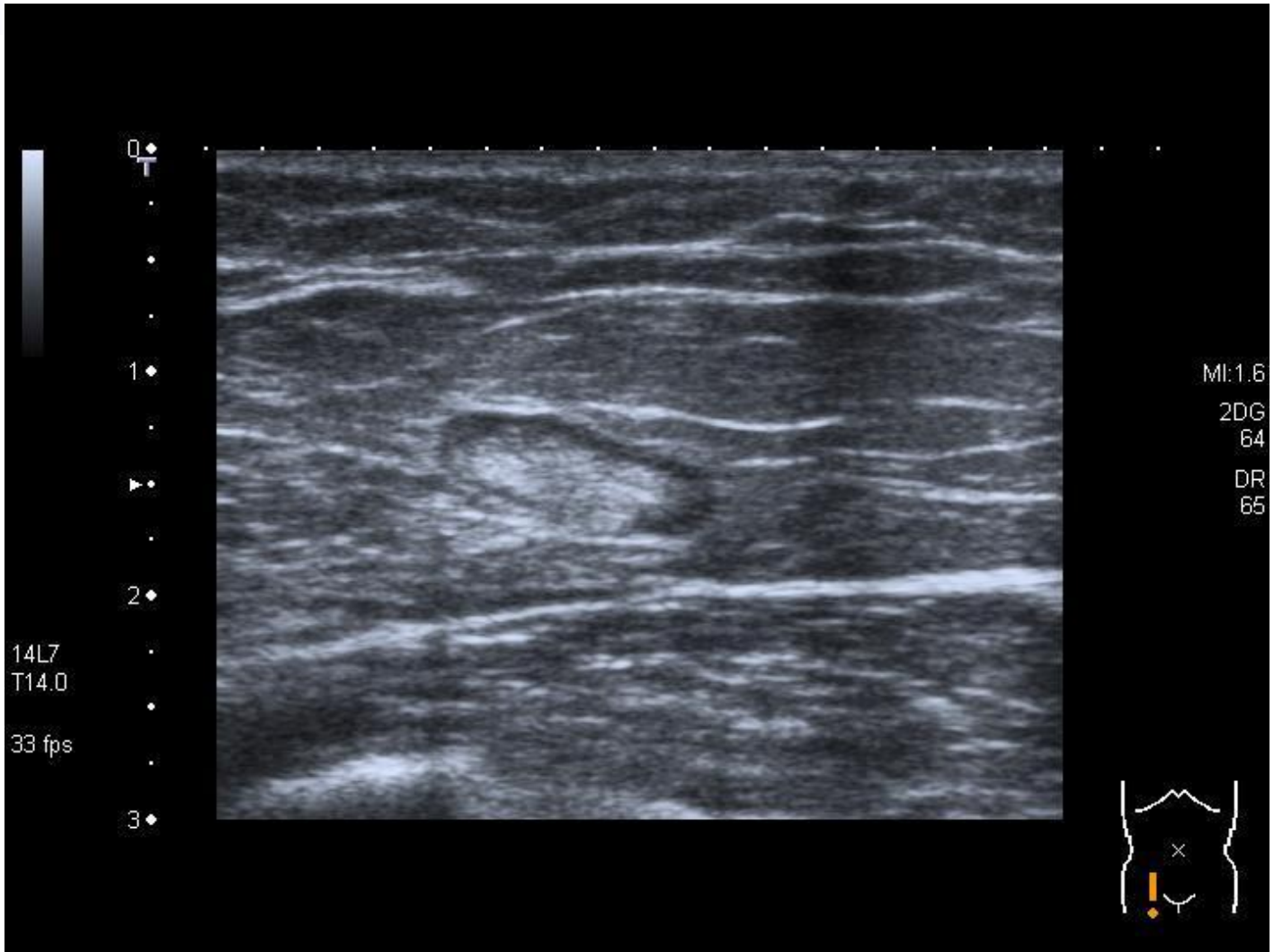


maligne benigne

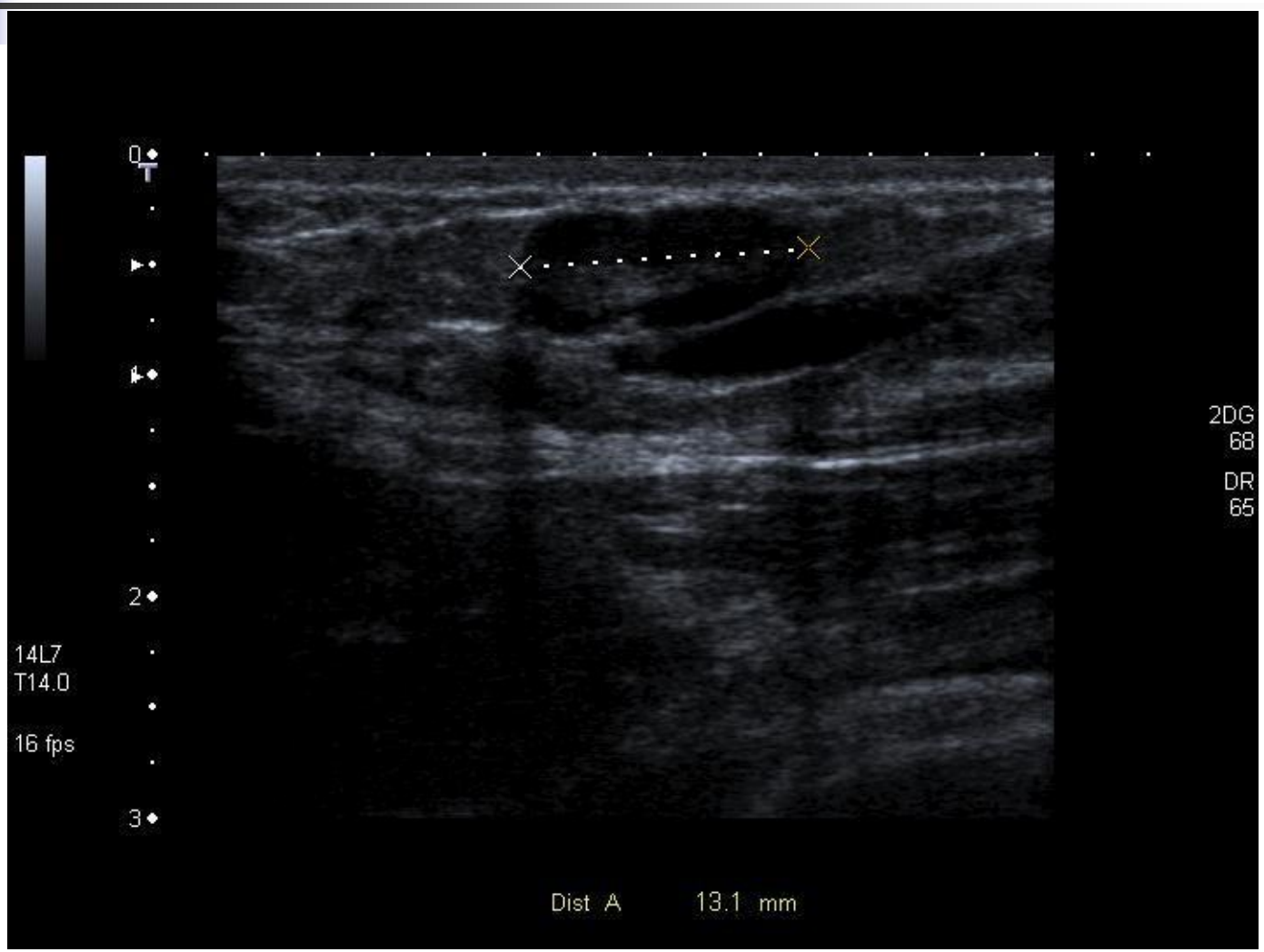
normal lymph nodes



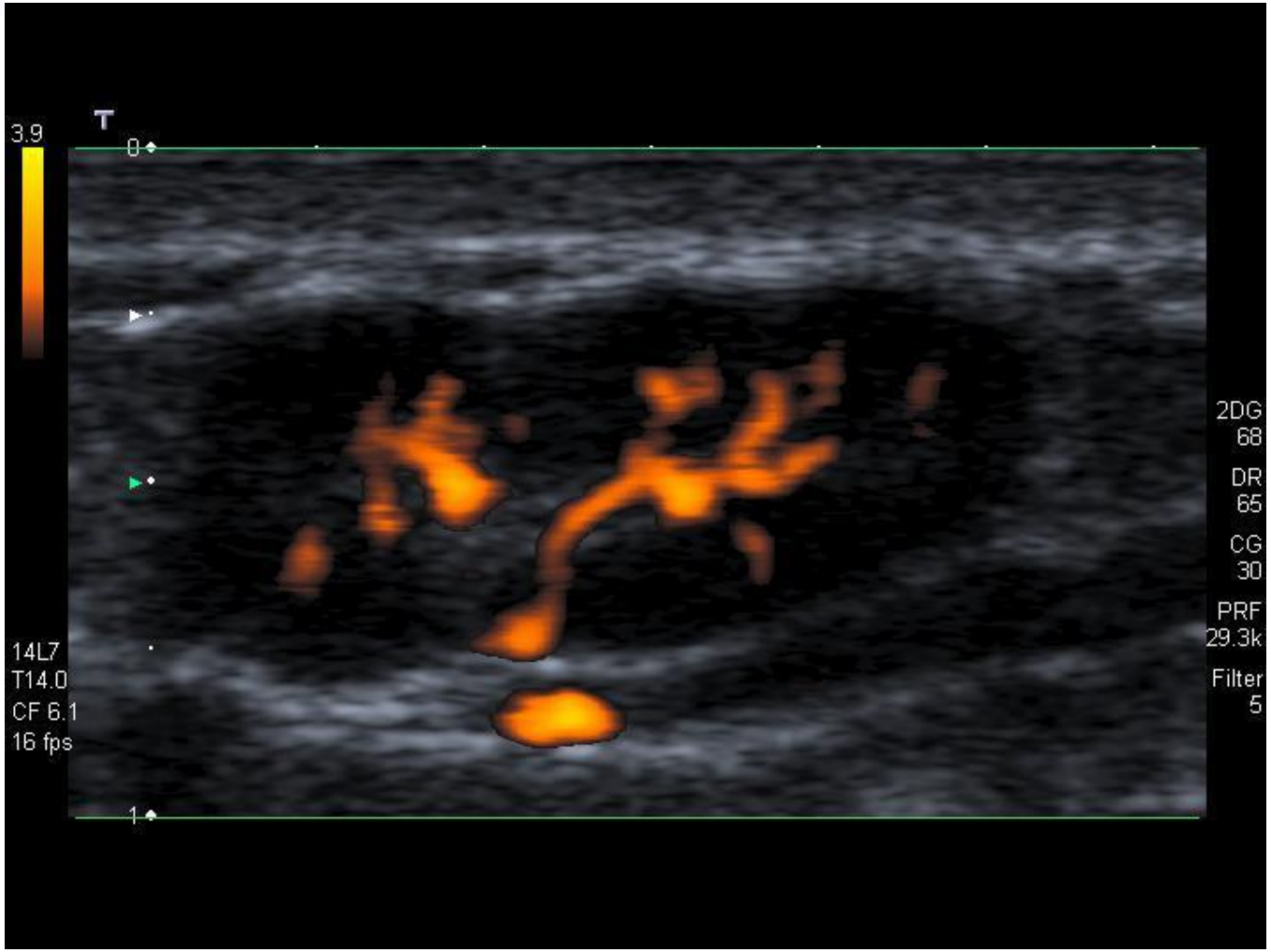
normal lymph nodes



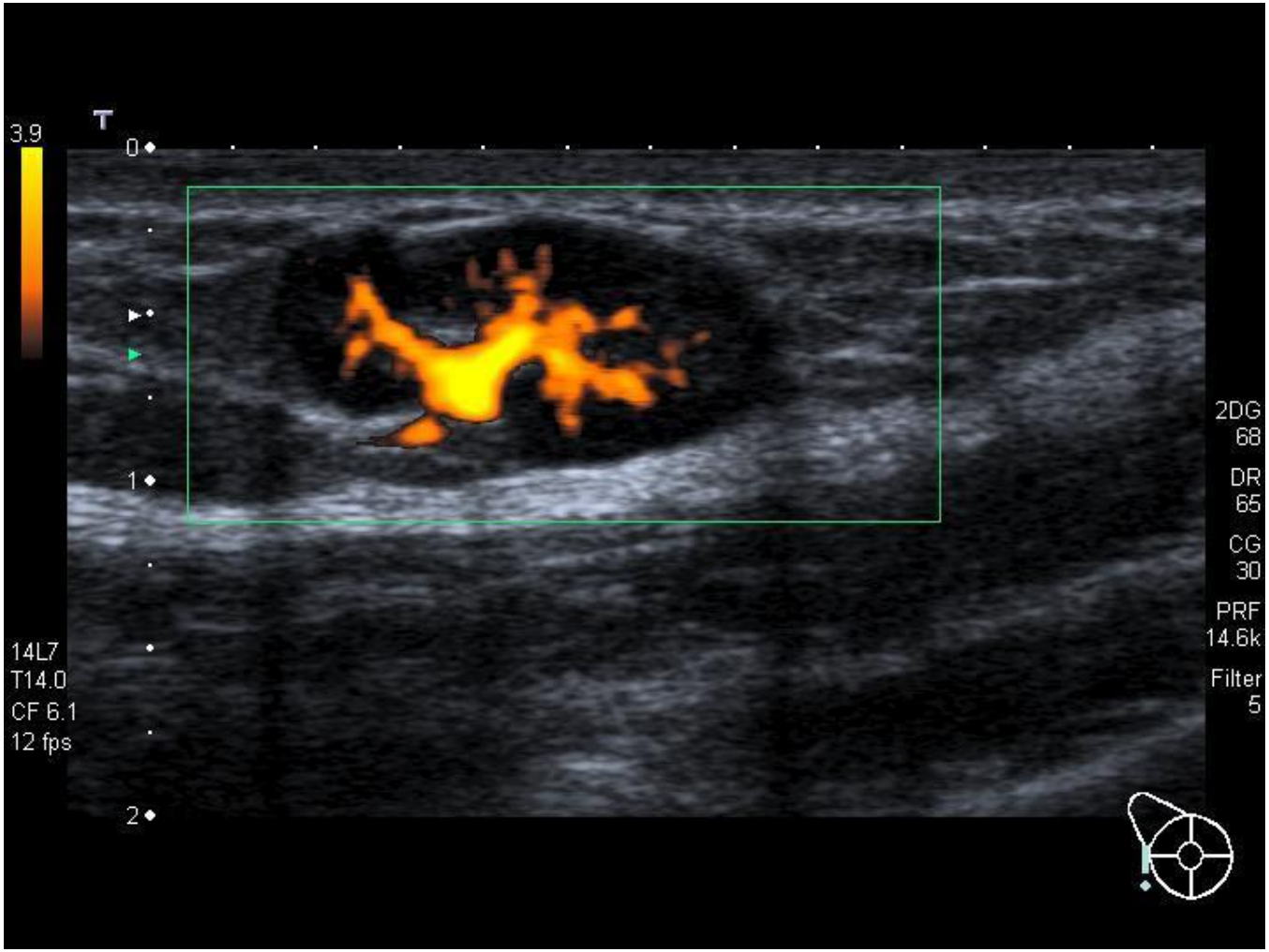
normal lymph nodes



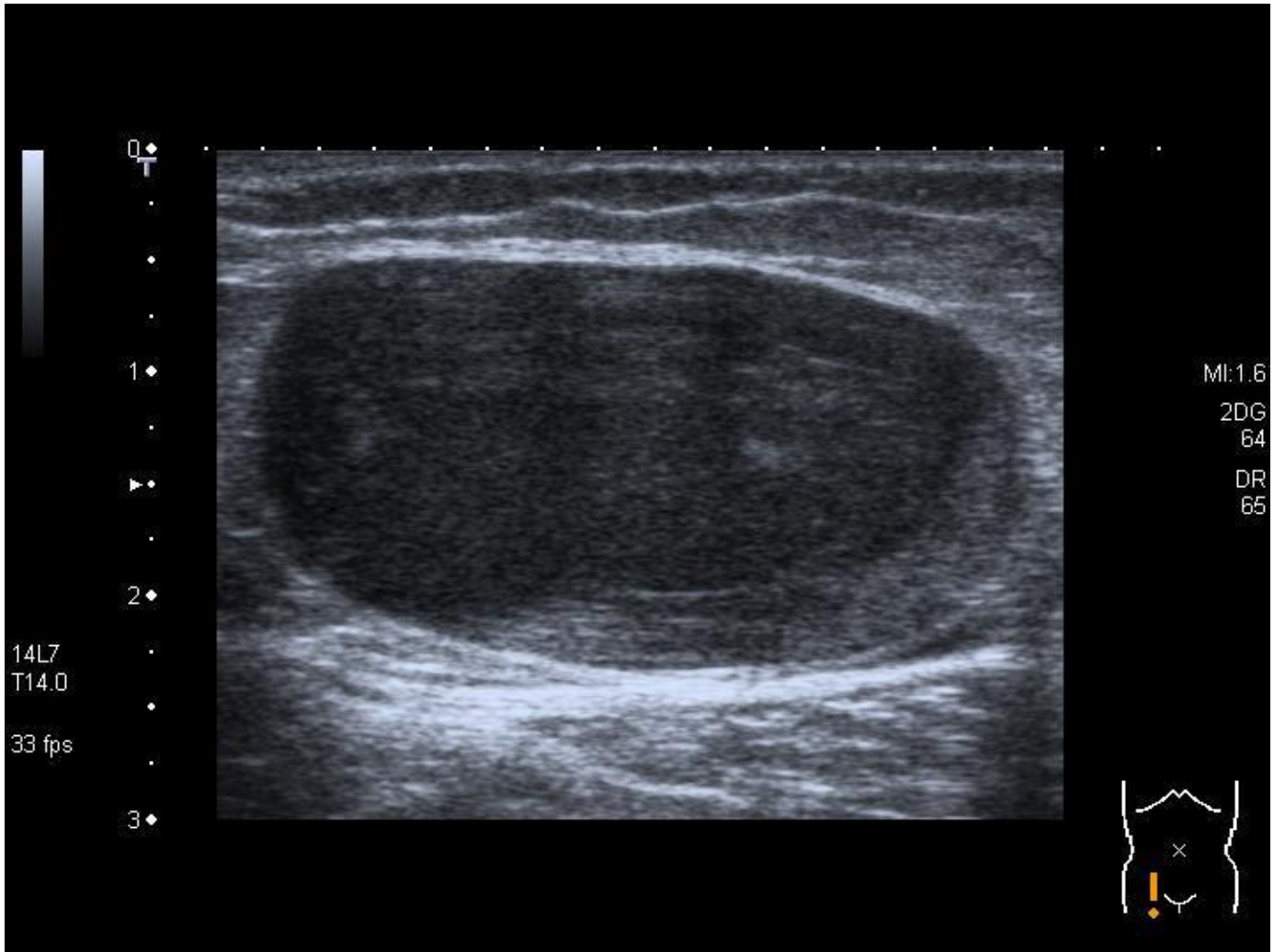
normal lymph nodes



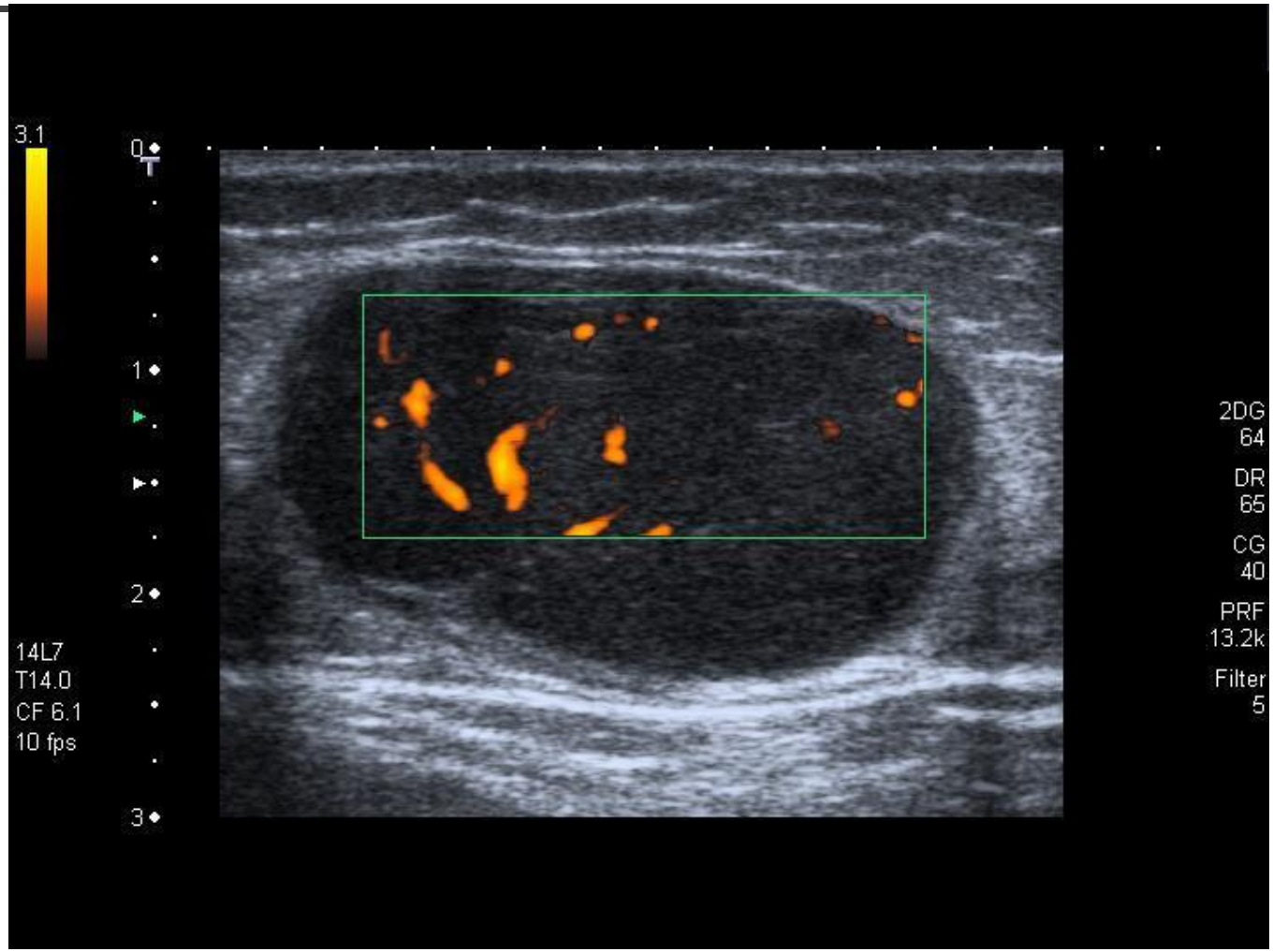
normal lymph nodes



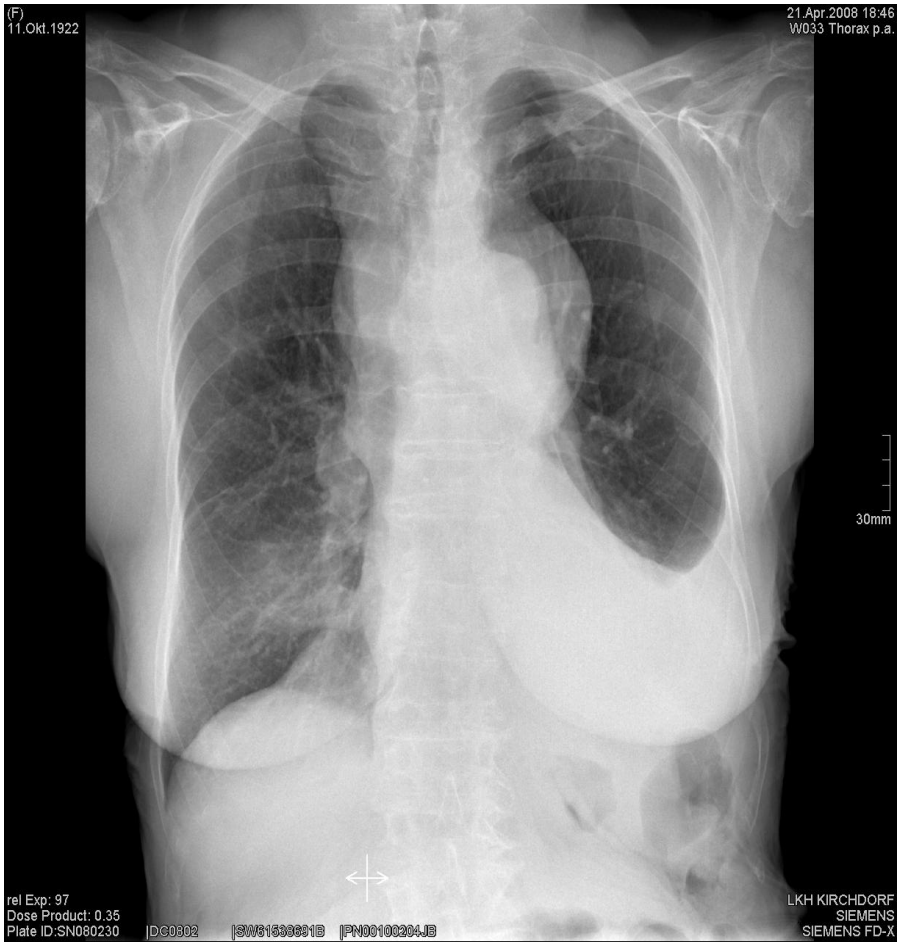
malignant lymph node (Hodgkin's disease)



malignant lymph node (Hodgkin's disease)



chest x-ray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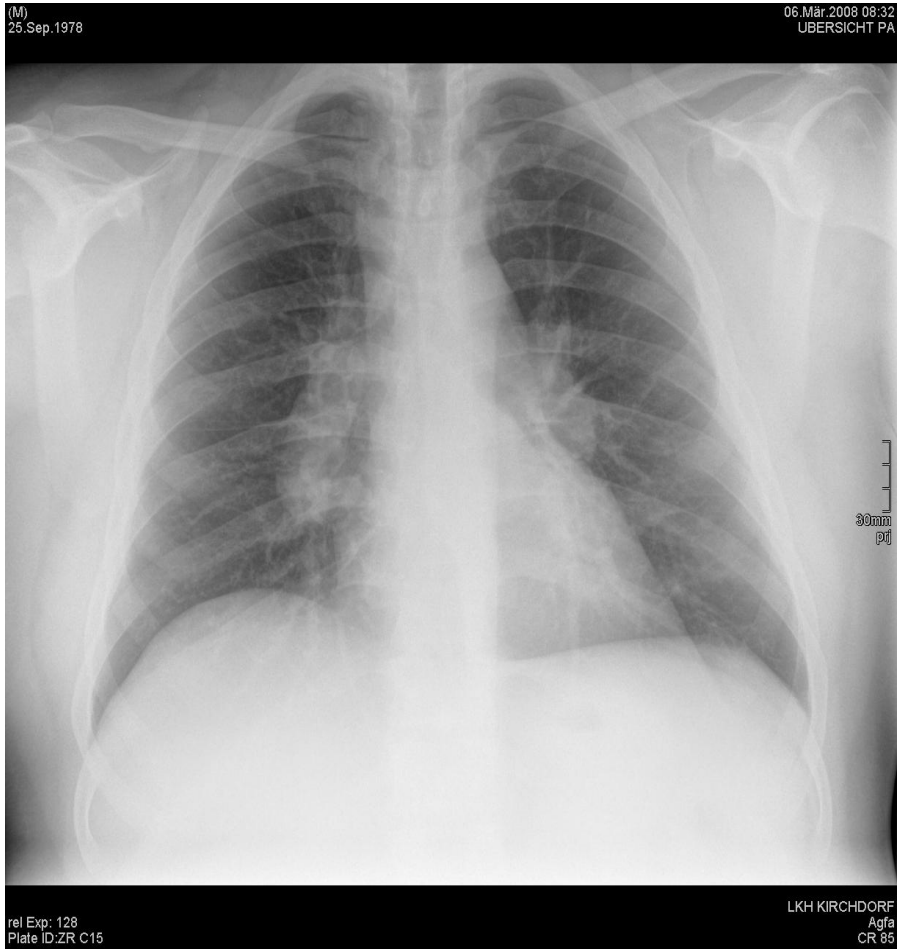
SIEMENS
SIEMENS FD-X

chest x-ray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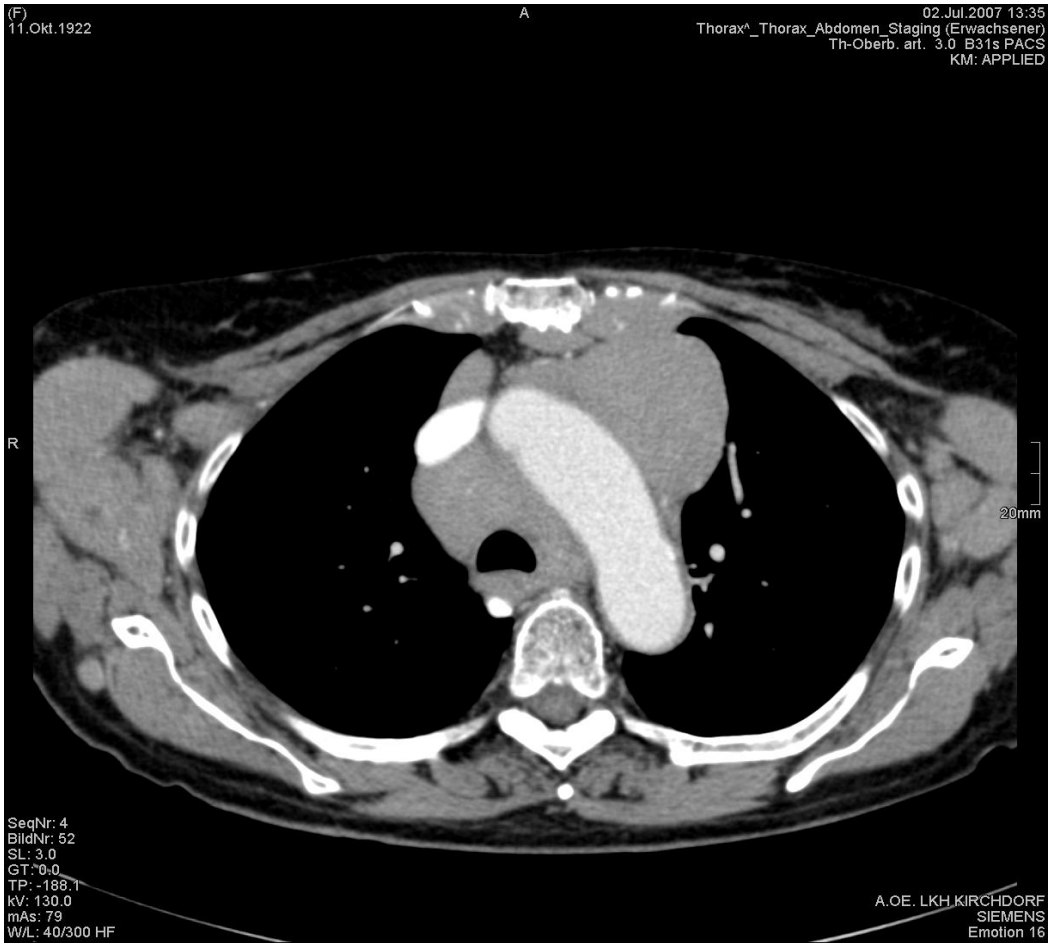
Agfa
CR 85

CT-scan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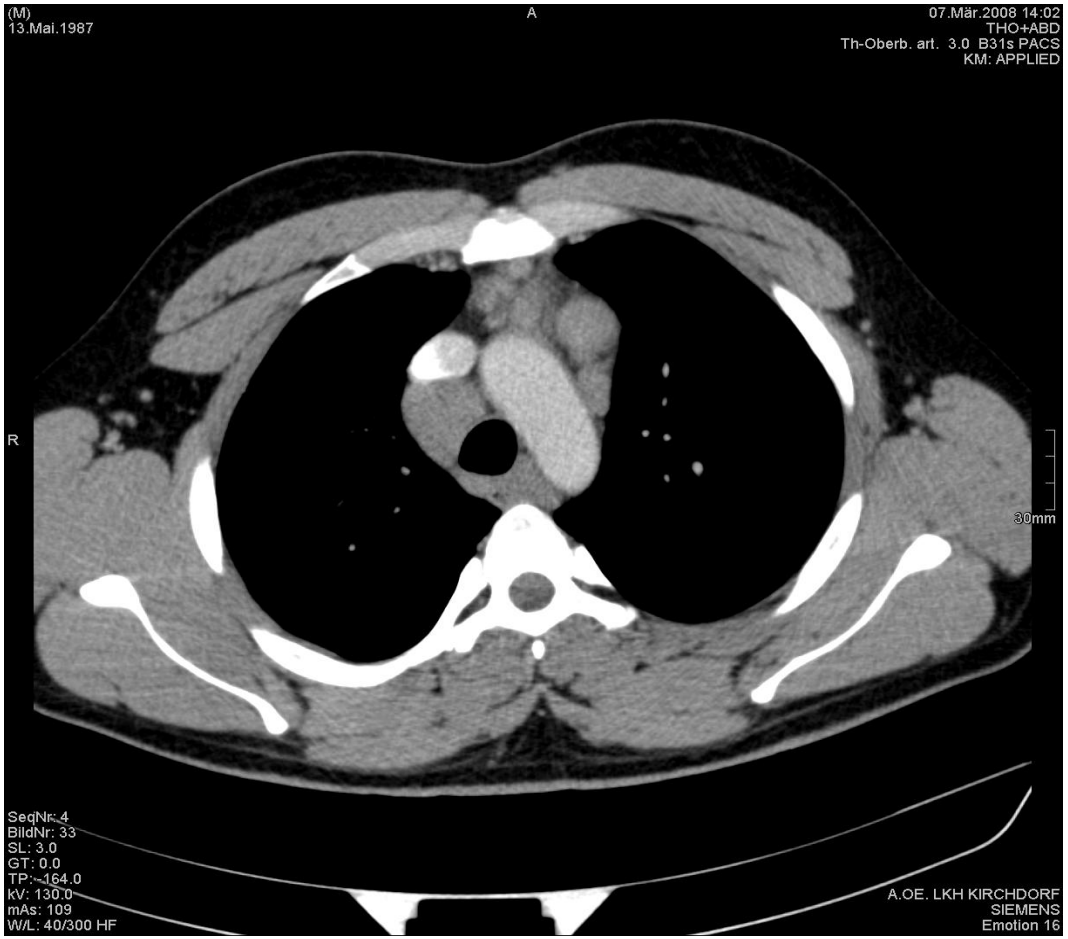
A.OE. LKH KIRCHDORF
SIEMENS
Emotion 16

CT-scan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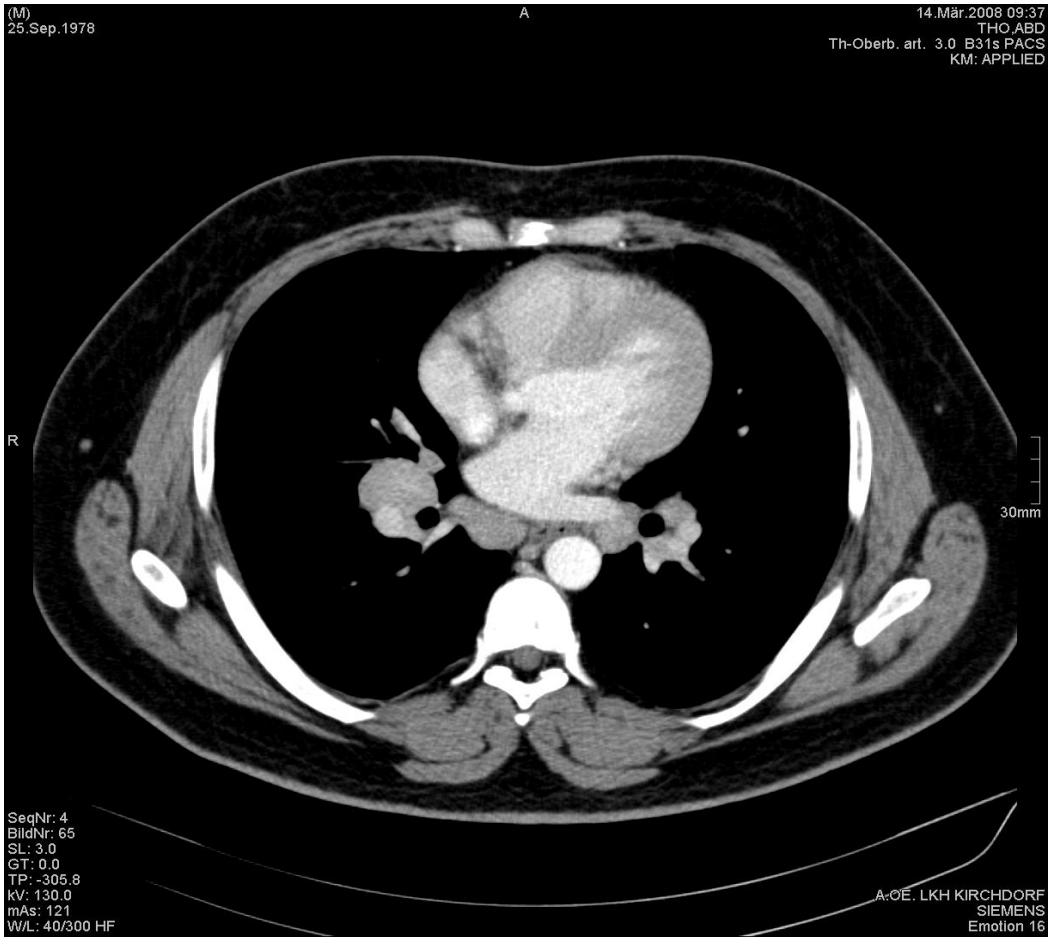
SIEMENS
Emotion 16

CT-scan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A:OE. LKH KIRCHDORF
SIEMENS
Emotion 16

DIFFERENTIAL DIAGNOSES

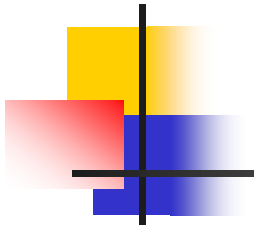
lymph node < 1 cm^2 (US): benigne

lymph node > 2 cm (US): malignant or granulomatous lymphadenopathy (tuberculosis, sarcoidosis, brucellosis, tularemia)

lymph node >2,25 cm^2 (1,5 cm x1,5 cm): malignant or granulomatous lymphadenopathy

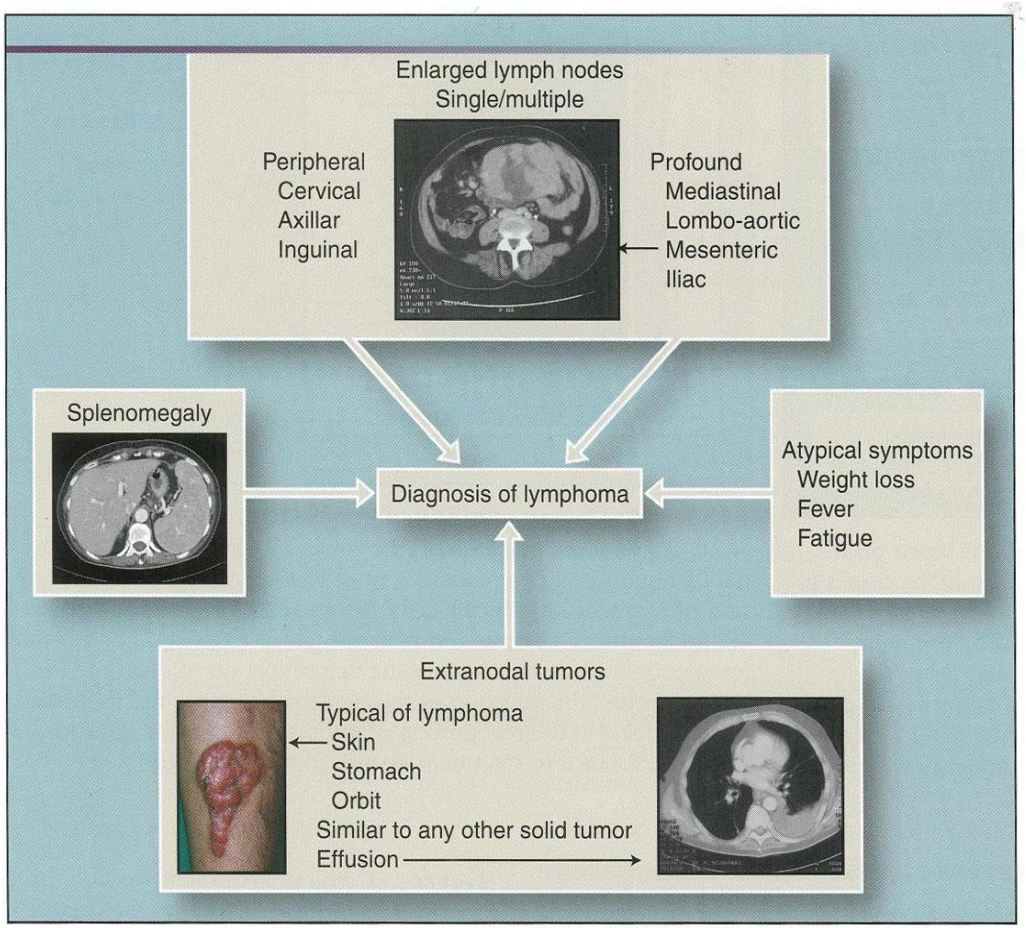
lymph nodes <1 cm^2 after excluding infectious mononucleosis/toxoplasmosis observation unless there are symptoms and signs of an underlying systemic illness.

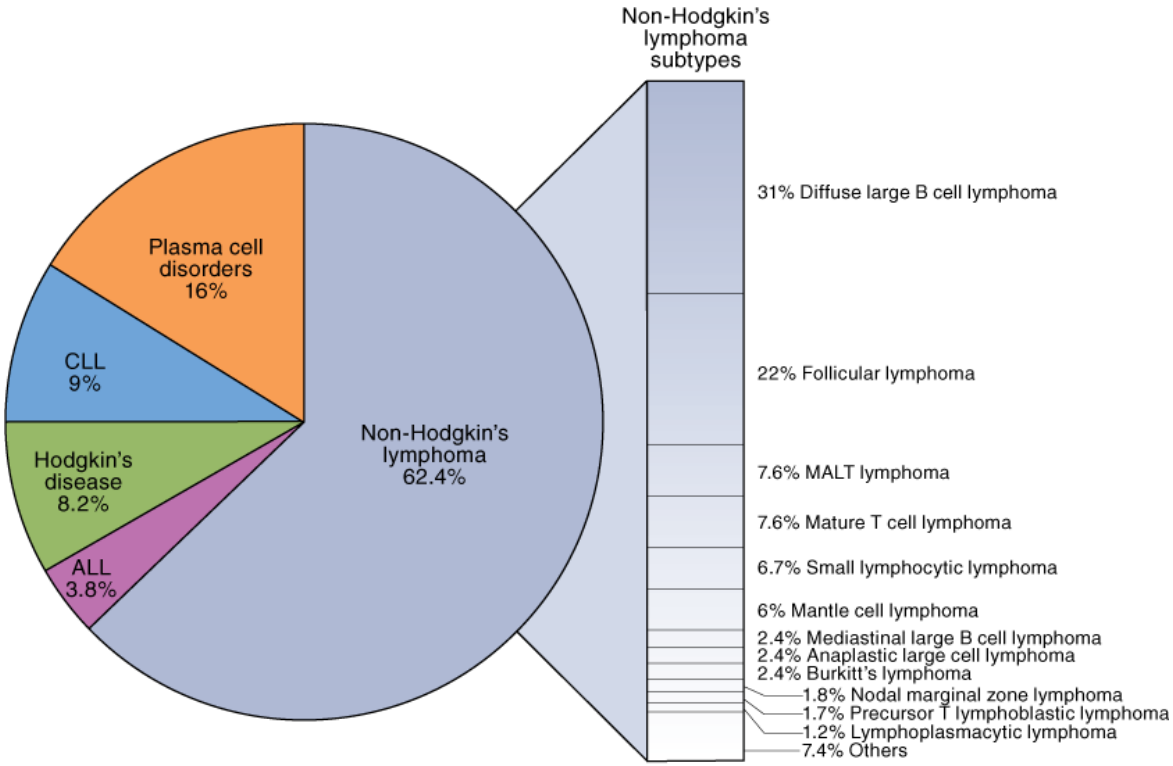
enlarged intraabdominal or retroperitoneal nodes are usually malignant (usually lymphomas or germ cell tumors in young men; very rare tuberculosis of mesenterical lymph nodes)



LYMPHOMAS

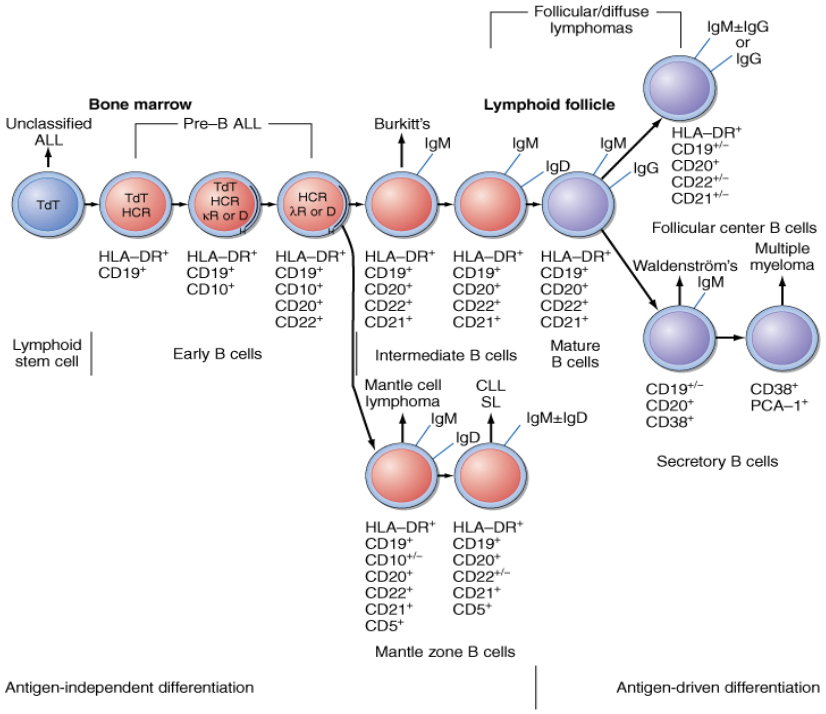
Lymphomas


Enlarged lymph nodes
Single/multiple
Peripheral
Cervical
Axillar
Inguinal
Profound
Mediastinal
Lombo-aortic
Mesenteric
Iliac
Splenomegaly
Diagnosis of lymphoma
Atypical symptoms
Weight loss
Fever
Fatigue
Extranodal tumors
Typical of lymphoma
Skin
Stomach
Orbit
Similar to any other solid tumor
Effusion

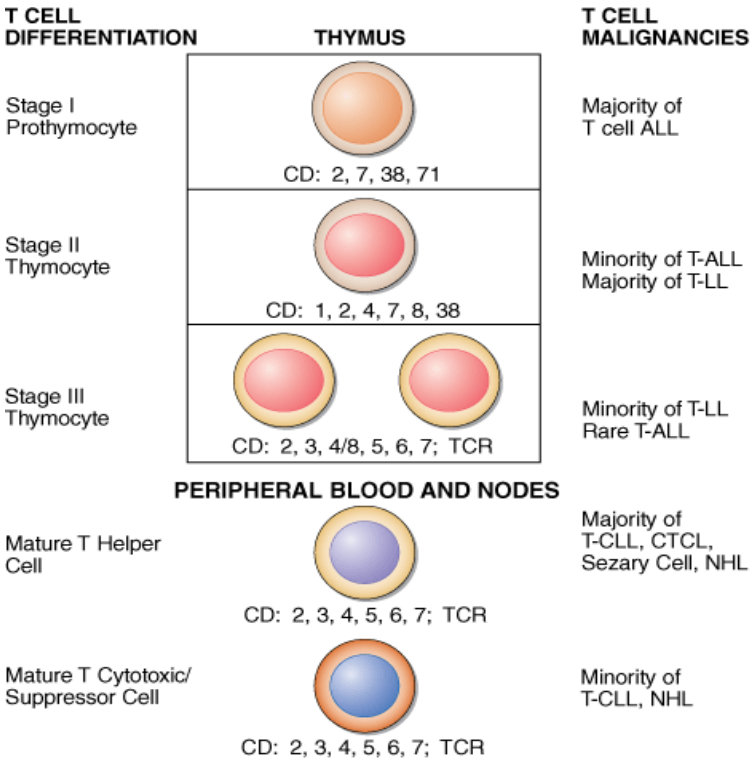


Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

normal B cell differentiation and relationship to B cell lymphomas



normal T cell differentiation and relationship to T cell lymphomas



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

B cell lymphomas
diagnosis by CD antigen expression

Neoplasm	sIg; cIg	CD5	CD10	CD23	CD43	CD103	BCL6	IRF4/ MUM1	Cyclin D1	ANXA1
CLL/SLL	+;-/+	+	-	+	+	-	-	(+PC)	-	-
LPL	+/-;+	-	-	-	-/+	-	-	+*	-	-
Splenic MZL	+;-/+	-	-	-	-	-	-	-	-	-
HCL	+;-	-	-	-	-	+	-	-	+/-	+
Plasma cell myeloma	-;+	-	-/+	-	-/+	-	-	+	-/+	-
MALT lymphoma	+;+/-	-	-	-/+	-/+	-	-	+*	-	-
Follicular lymphoma	+;-	-	+/-	-/+	-	-	+	-/+#	-	-
MCL	+;-	+	-	-	+	-	-	-	+	-
Diffuse large B-cell lymphoma	+/-;-/+	-***	-/+##	NA	-/+	NA	+/-##	+/-**	-	-
Burkitt lymphoma	+;-	-	+	-	+/-	NA	+	-/+	-	-

+, >90% of cases +; +/-, >50% of cases +; -/+, <50% of cases +; -, <10% of cases +. IRF4/MUM1, interferon regulating factor 4; ANXA1, Annexin A1; PC, proliferation centres; *, plasma cell component positive; #, some grades 3a and 3b; ##, DLBCL of germinal centre B-cell type (GCB) express CD10 and BCL6; **, DLBCL of activated B-cell type (ABC) are typically positive for IRF4/MUM1; ***, some DLBCL are CD5+; NA, not applicable; LPL, lymphoplasmacytic lymphoma; MZL, marginal zone lymphoma; MCL, mantle cell lymphoma.

Table 1. Selected Examples of Chromosomal Rearrangements.*

Genetic Change†	Gene Fusion	Disease	Targeted Therapy‡
Formation of chimeric fusion genes			
Involving tyrosine kinases			
inv(2)(p22-p21p23)§	*EML4-ALK*	Non–small-cell lung cancer	
t(2;5)(p23;q35)	*ALK-NPM1*	Anaplastic large-cell lymphoma	
t(4;14)(p16.3;q32.33)§	*WHSC1-IGHG1*	Multiple myeloma	
del(4)(q12q12)§	*FIP1L1-PDGFRA*	Myeloid neoplasm associated with eosinophilia	Imatinib
t(5;12)(q31-q32;p13)	*PDGFRB-ETV6*	Myeloid neoplasm associated with eosinophilia	Imatinib
t(9;22)(q34.1;q11.23)	*BCR-ABL1*	Chronic myeloid leukemia, acute lymphoblastic leukemia, acute myeloid leukemia	Imatinib, dasatinib, nilotinib
episome(9q34.1)§	*NUP214-ABL1*	Acute lymphoblastic leukemia	Imatinib
inv(10)(q11.2q11.2)§	*RET-NCOA4*	Papillary thyroid cancer	
inv(10)(q11.2q21)	*RET-CCDC6*	Papillary thyroid cancer	
t(12;15)(p13;q25)	*ETV6-NTRK3*	Various cancers	

Involving transcription factors			
t(1;22)(p13;q13)	*RBM15-MKL1*	Acute megakaryoblastic leukemia	
t(2;3)(q12-q14;p25)	*PAX8-PPARG*	Follicular thyroid cancer	
t(7;11)(p15-p14;p15.5)	*NUP98-HOXA9*	Myelodysplastic syndrome, acute myeloid leukemia	
t(8;21)(q22;q22.3)	*RUNX1-RUNX1T1*	Acute myeloid leukemia	
t(9;11)(p22;q23)	*MLL-MLLT3*	Acute myeloid leukemia	
t(11;22)(q24.1-q24.3;q12.2)	*FLI1-EWSR1*	Ewing's sarcoma	
t(12;21)(p13;q22.3)§	*ETV6-RUNX1*	Acute lymphoblastic leukemia	
t(15;17)(q22;q21)	*PML-RARA*	Acute promyelocytic leukemia	All-*trans* retinoic acid, arsenic trioxide
inv(16)(p13.11q22.1)	*CBFB-MYH11*	Acute myeloid leukemia	
t(21;22)(q22.3;q12.2)	*ERG-EWSR1*	Ewing's sarcoma	
Deregulated expression of structurally normal genes			
t(8;14)(q24.21;q32.33)	*MYC-IGHG1*	Burkitt's lymphoma	
t(11;14)(q13;q32.33)	*CCND1-IGHG1*	Mantle-cell lymphoma	
t(12;13)(p13;q12.3)	*ETV6-CDX2*	Acute myeloid leukemia	
t(14;18)(q32.33;q21.3)	*IGHG1-BCL2*	Follicular lymphoma	
del(21)(q22.3q22.3)§	*TMPRSS2-ERG*	Prostate cancer	

* The full names of all genes that are listed according to their abbreviations appear in a glossary in the Supplementary Appendix.
† Chromosomal localizations are in accordance with the genome mapping data provided in the National Center for Biotechnology Information (NCBI) Map Viewer (build 36.3; www.ncbi.nlm.nih.gov/mapview).
‡ Imatinib has not been approved for treatment of myeloid neoplasms associated with eosinophilia and *NUP214-ABL1*–positive acute lymphoblastic leukemia, but therapeutic efficacy is predicted on the basis of preclinical studies. The other drugs listed have been approved for treatment of the indicated tumor types.
§ This cryptic alteration is cytogenetically invisible.

Viruses and Other Pathogens Involved in the Development of Lymphomas

Pathogens	Lymphomas Associated with Virus	Putative Mechanisms Leading to Lymphoma
HIV	Diffuse large B-cell lymphoma [11] Burkitt's lymphoma Castleman disease Hodgkin lymphoma	Depression of immune functions with activation of *c-MYC*, inactivation of *p53*, and infection with EBV [12]
Human T-cell leukemia/lymphoma virus	ATL	Inactivation of tumor suppressor genes mediated by Tax [13]
EBV	Burkitt's lymphoma T-NK-cell lymphoma (nasal type) Posttransplant lymphomas	Chronic latent infection with encoding of two proteins that inhibit apoptosis (BHFR1 and LMP-1)
HHV-8	Kaposi sarcoma Primary effusion lymphoma Castelman disease	Coinfection with EBV Viral protein expression
HCV	Splenic marginal zone lymphoma Mixed cryoglobulinemia [14]	Unconvincing evidence [15]
SV40	Diffuse large B-cell lymphoma Follicular lymphoma [16]	Inactivation of *rb* and *p53* genes
Helicobacter pylori	Gastric MALT lymphoma [17]	Chronic antigen stimulation followed by secondary activation of NF-κB pathway [18]
Borrelia burgdorferi	Cutaneous MALT lymphoma [19]	

MALIGNANT LYMPHOMAS

indolent generalized lymphadenopathy

Indolent Non Hodgkin's lymphomas (slowly progredient)

- follicular lymphoma
- chronic lymphocytic leucemia

In 80 % at diagnosis stage III – IV (Ann Arbor-Classification)

Stadieneinteilung nach der Ann Arbor-Klassifikation (1971)

Stadium	Definition
I	Nodaler Befall einer einzelnen Lymphknotenregion (I) oder Vorliegen eines einzelnen, lokalisierten extranodalen Herdes (I_E)
II	Nodaler Befall (II) und/oder lokalisierte extranodale Herde (II_E) in $\geq$ 2 Regionen auf einer Seite des Zwerchfells
III	Nodaler Befall (III) und/oder lokalisierte extranodale Herde (III_E) auf beiden Seiten des Zwerchfells, ggf. mit Milzbefall (III_S oder III_{SE})
IV	Diffuser oder disseminierter Befall eines oder mehrerer extralymphatischer Organe mit oder ohne Lymphknotenbefall
A	keine Allgemeinsymptome
B	Allgemeinsymptome (Fieber > 38 °C, Nachtschweiß, Gewichtsverlust ≥ 10 % des Ausgangsgewichts in 6 Monaten)

Staging of CLL by RAI (1975, 1987) and Binet (1981)

Risiko	Stadium	Definition	Überleben[1]
Niedrig	0	Lymphozytose ≥ 5000/µl Knochenmark-Infiltration > 30 %	≥ 12,5 Jahre
Mittel	I	Lymphozytose + Lymphadenopathie	8,5 Jahre
	II	Lymphozytose + Splenomegalie und/oder Hepatomegalie (mit oder ohne Lymphadenopathie)	6 Jahre
Hoch	III	Lymphozytose + Anämie (Hämoglobin < 11 g/dl) (mit oder ohne Adenopathie/Organomegalie)	1,5 Jahre
	IV	Lymphozytose + Thrombozytopenie (Thrombozyten < 100 000/µl) (mit oder ohne Anämie/Adenopathie/Organomegalie)	1,5 Jahre

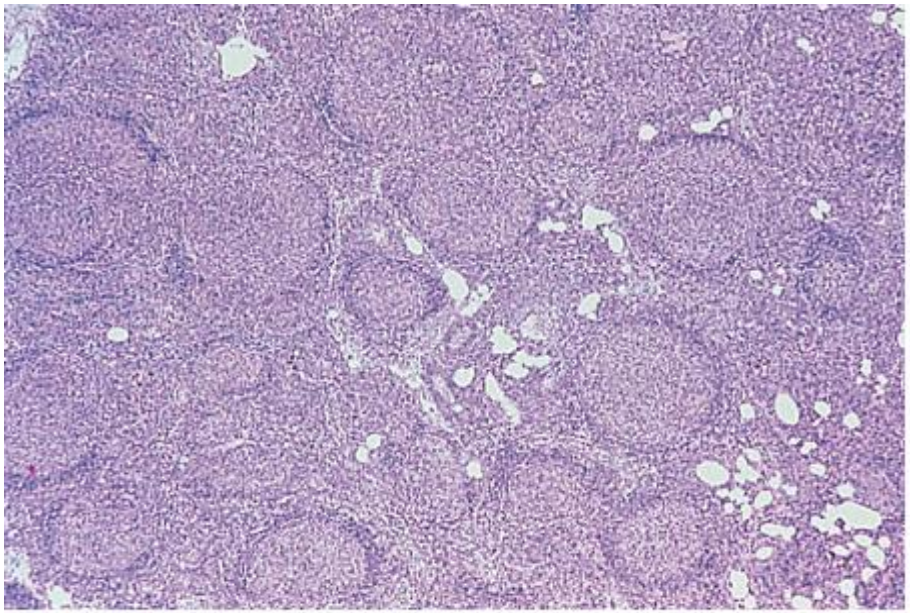
[1] medianes Überleben

Stadieneinteilung nach Binet (1981)

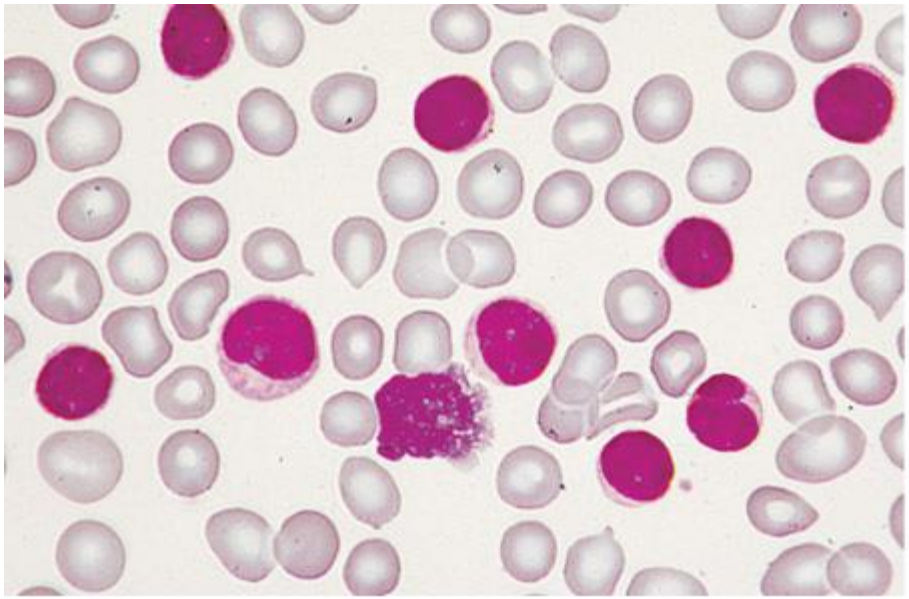
Risiko	Stadium	Lymphadenopathi[2]	Hämoglobin (g/dl)	Thrombozyten (/µl)	Überleben[1]
Niedrig	A	< 3	> 10	normal	> 10 Jahre
Mittel	B	≥ 3	> 10	normal	5 Jahre
Hoch	C	unabhängig	< 10	< 100 000	2 Jahre

[1] medianes Überleben [2] Anzahl befallener Lymphknotenregionen

follicular lymphoma



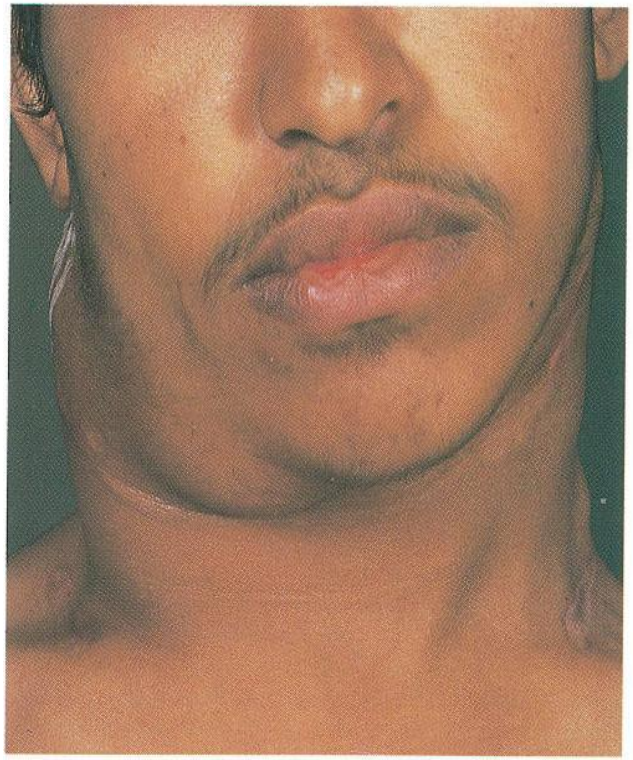
chronic lymphocytic leukaemia



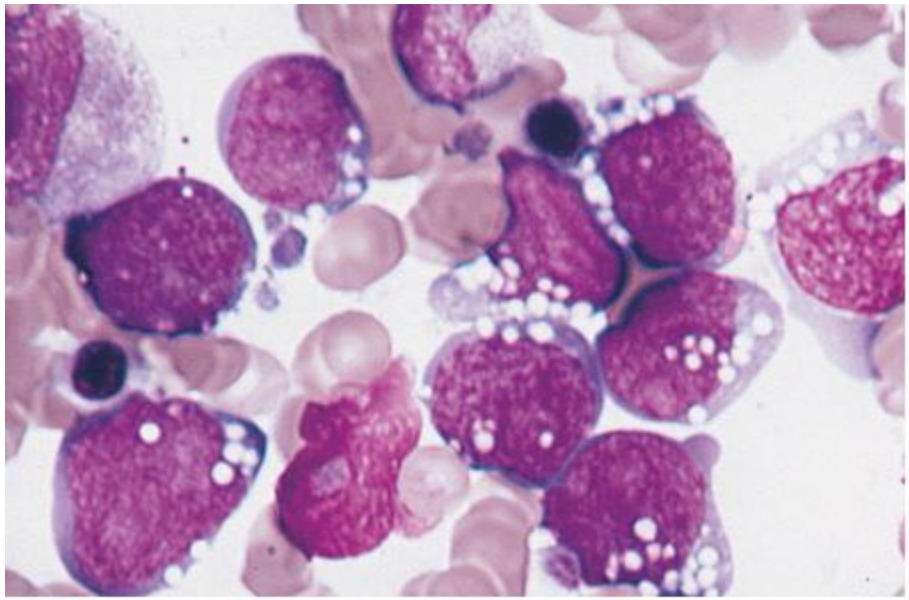
AGGRESSIVE NON HODGKIN's LYMPHOMAS

B-symptomatic, rapid enlargement of lymph nodes

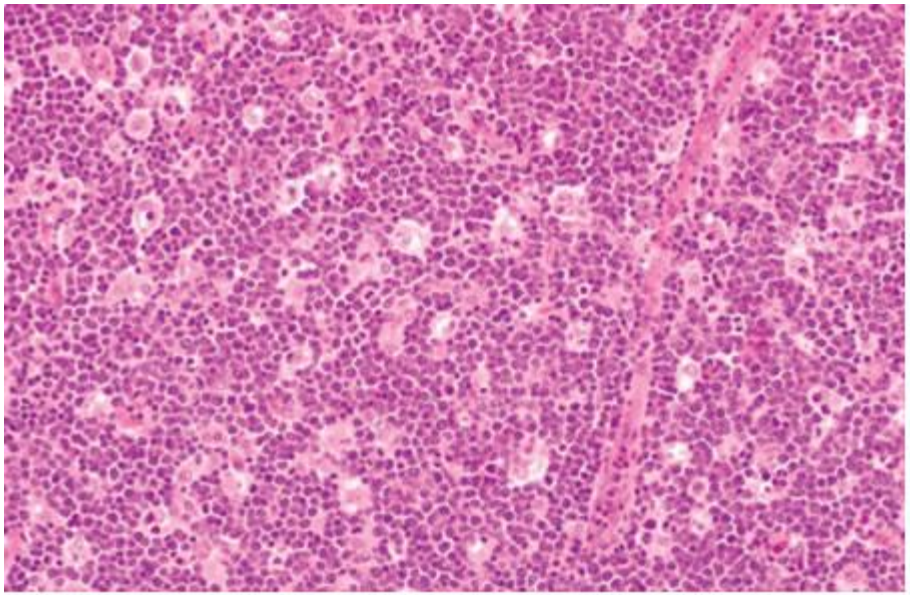
- diffuse large B cell lymphoma (DLBCL)
- Burkitt's lymphoma



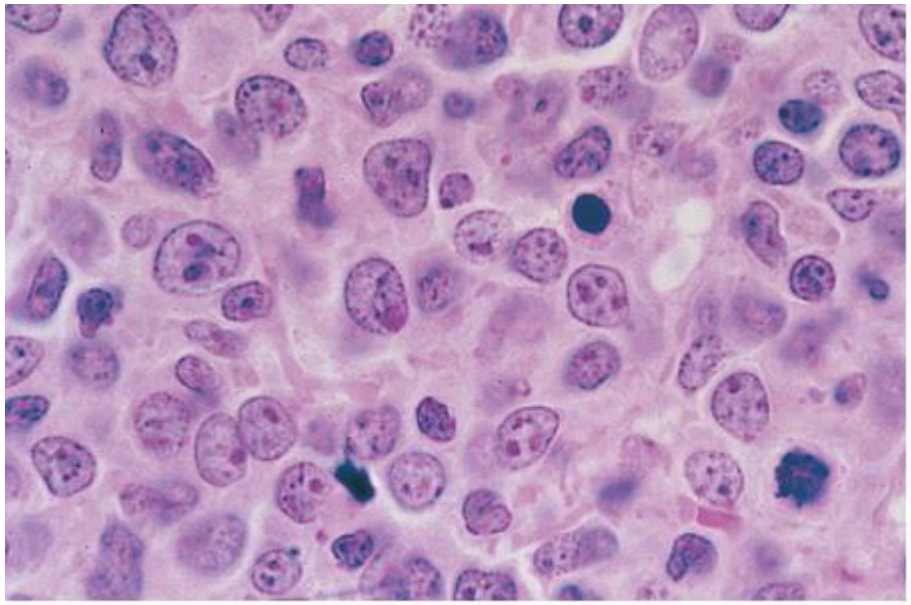
Burkitt's lymphoma



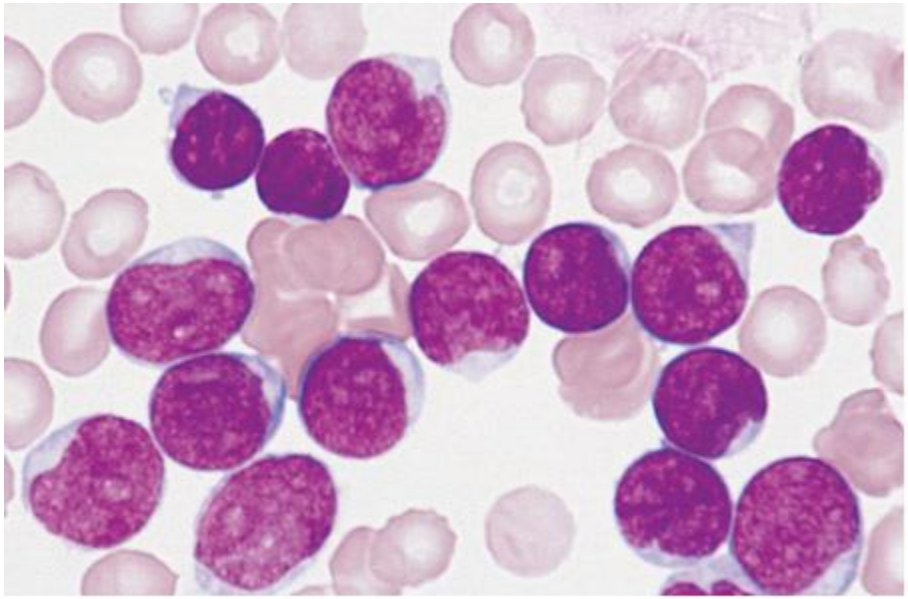
Burkitt's lymphoma



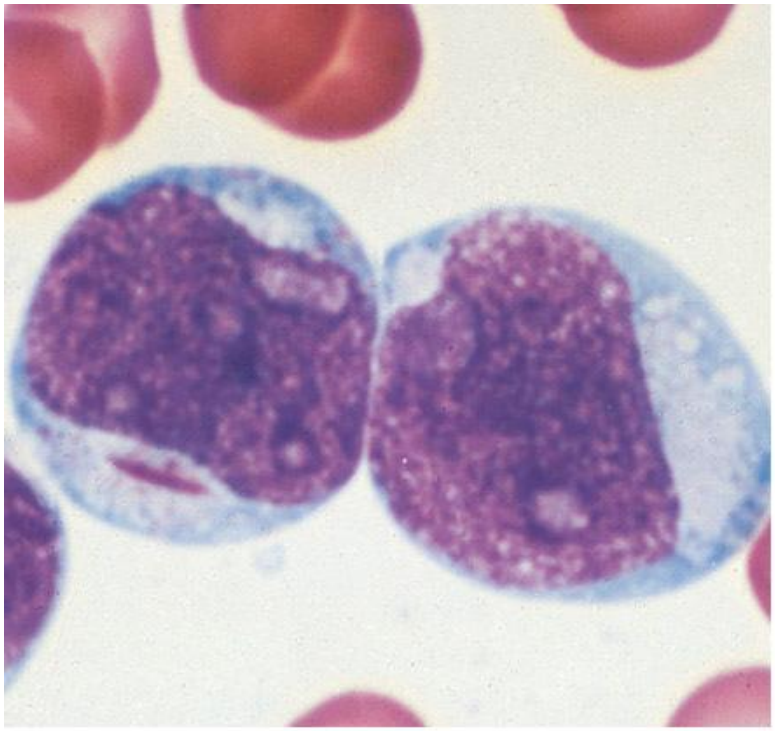
diffuse large B cell lymphoma



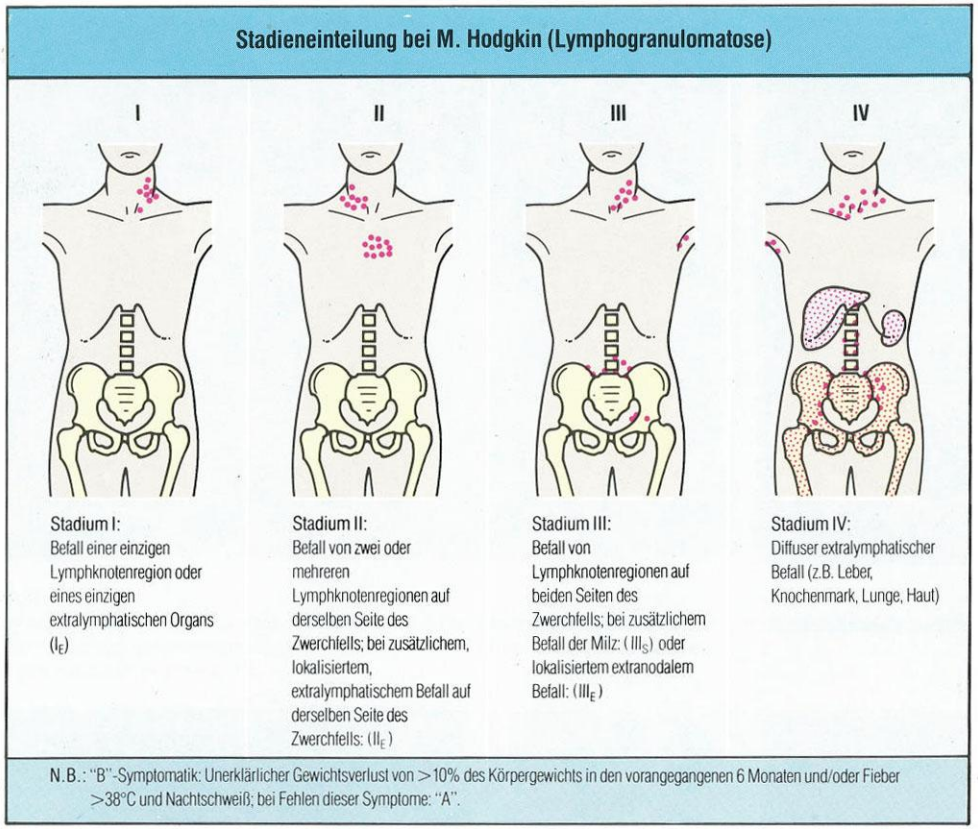
acute lymphoblastic leukaemia



acute myeloid leukaemia



Hodgkin's disease (Ann Arbor Staging System)



LYMPHADENOPATHY IN INFECTIOUS DISEASES

(children, young adults)

EBV-Infection: splenomegaly, lymphocytosis

CMV

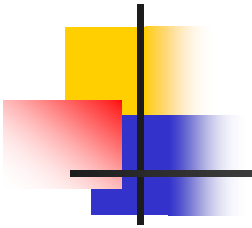
Influenca

viral hepatitis

german measels

Varicella

HIV



LYMPHADENOPATHY IN INFECTIOUS DISEASES

local infections (throat)

cat-scratch disease

tularemia (*Francisella tularensis*)

brucellosis (*Brucella melitensis*)

secundary Syphillis (rash)

gonorrhoea

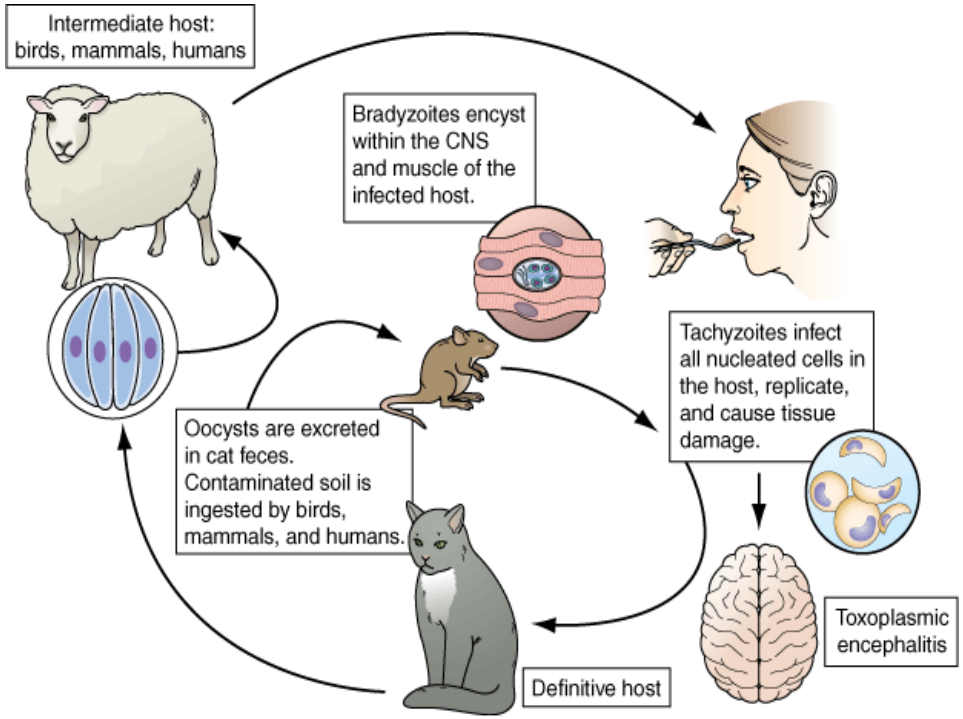
lymphogranuloma venereum (*Chlamydia trachomatis*)

lymphatic filariasis (*Wuchereria bancrofti*)

tuberkulosis (*Mycobacterium tuberculosis*)

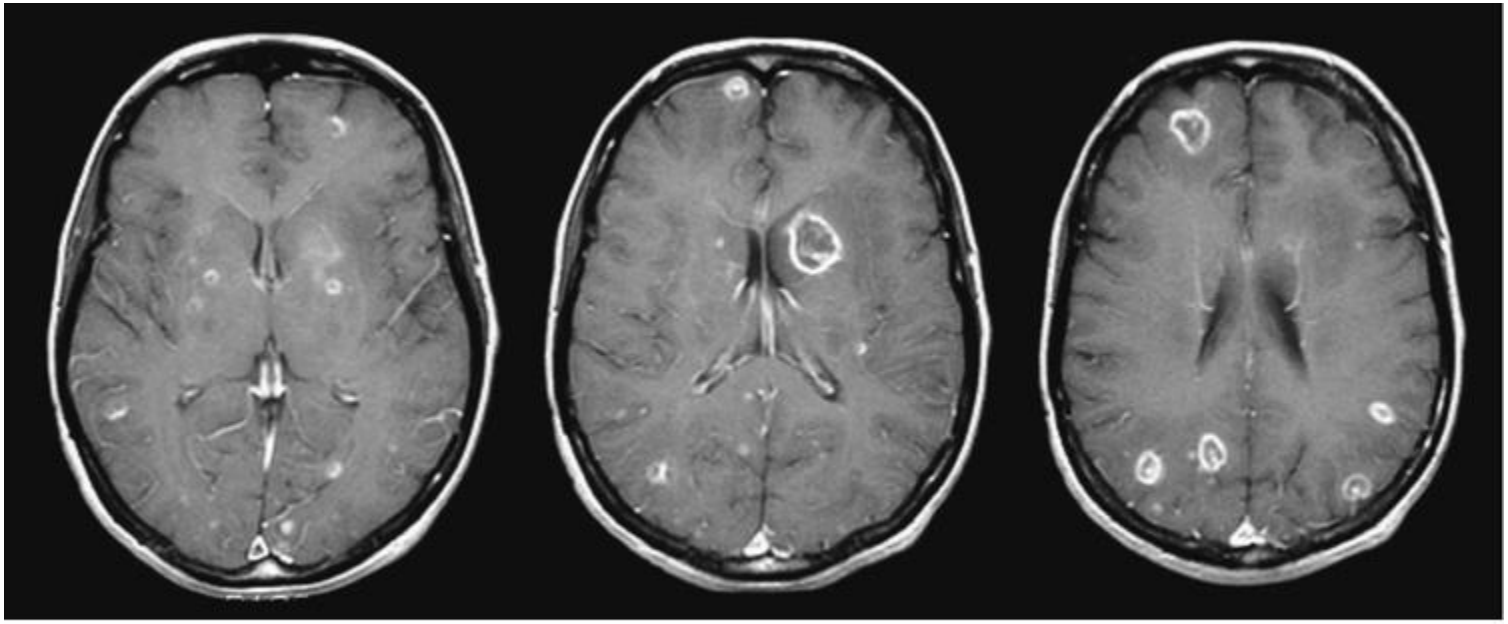
coccidioidomycosis/histoplasmosis

toxoplasmosis



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

toxoplasmosis



tuberculosis
scrofula

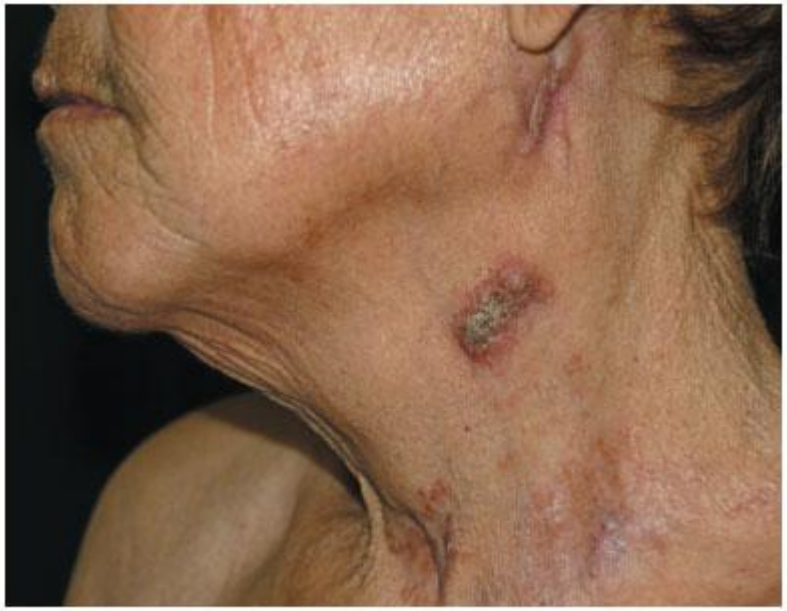
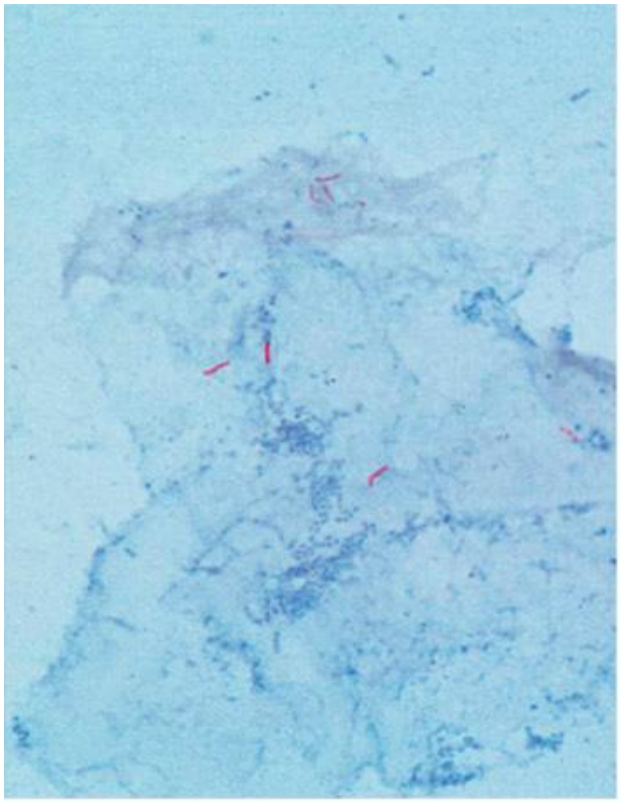


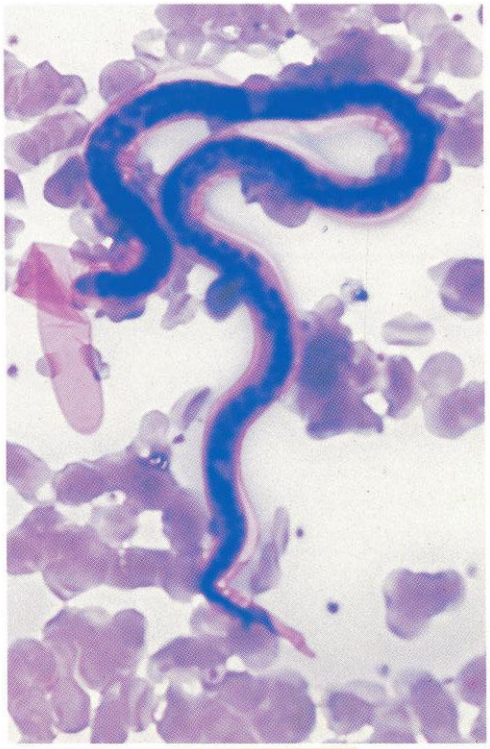
FIGURE 1: Erythematic lesions with hematic crusts covering fistulas in the left cervical region

tuberculosis, acid-fast bacillus smear

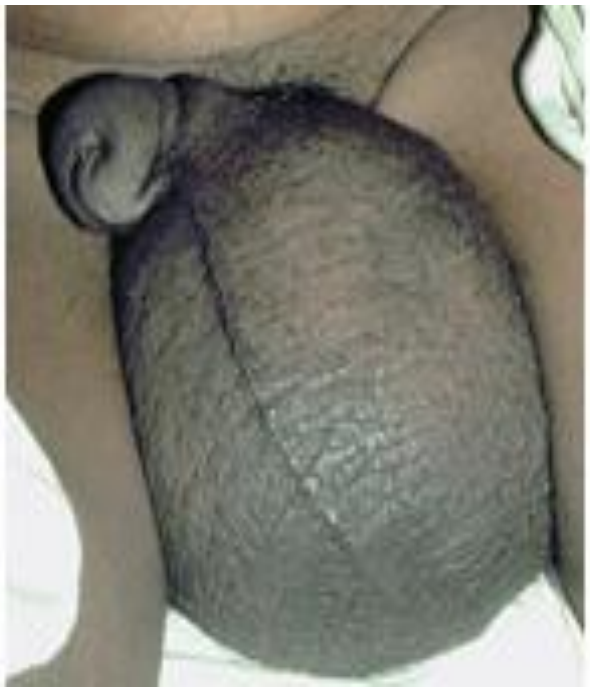


Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

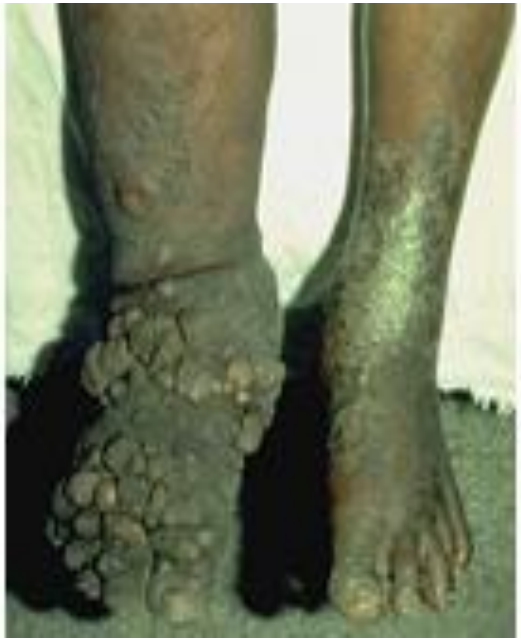
filariasis



filariasis



filariasis



LYMPHADENOPYTHY IN RHEUMATIC DISEASES

rheumatoid arthritis

Felty‘s syndrome:

generalized Lymphadenopathy

splenomegaly

leucopenia

thrombocytopenia

rheumatoid nodules typically found

Still‘s disease: (systemical manifestation of juvenile chronic arthritis)

acute febrile syndrome in young adults

transient maculopapular rash (salmon pink)

arthritis

marked leukocytosis (up to 60.000/µl)

lymphadenopathy

splenomegaly

hepatosplenomegaly

rare rheumatic nodules

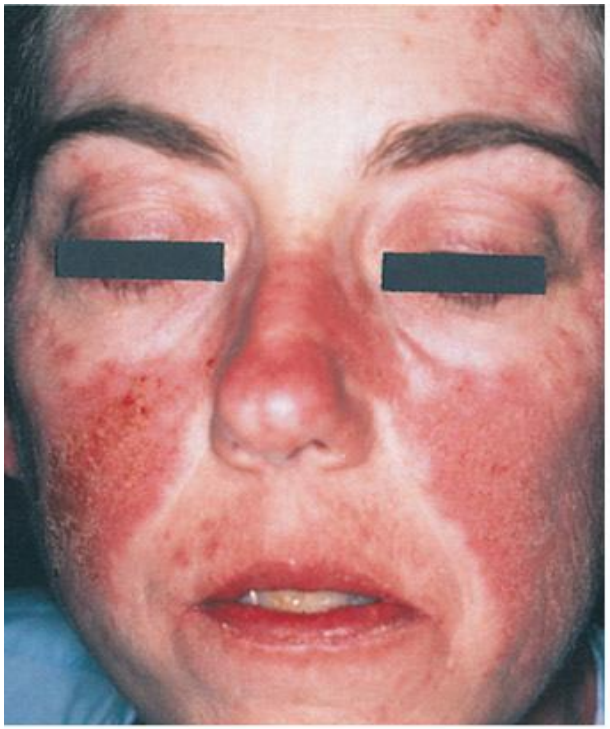
pleuritis, pericarditis, abdominal pain, sicca-syndrome, retinal exudates, iritis, peripheal neuropathy

LYMPHADENOPATHY IN RHEUMATIC DISEASES
DRUG INDUCED LYMPHADENOPATHY

systemic lupus erythematosus
Sjögren's syndrome
Hashimoto's thyreoiditis

drug induced lymphadenopathy:
carbamacepine, phenytoine, hydrochlorothiacid, allopurinol

systemic lupus erythematosus (malar erythema)



A

LYMPHADENOPATHY IN DISORDERS WITH UNKNOWN ETIOLOGY

Sarcoidosis: noncaseating granulomas (lung, ocular disease, erythema nodosum)

histiocytic necrotising lymphadenitis (Kikuchi-Fujimoto)

- cervical Lymphadenopathy, moderate fever (children and young adult)

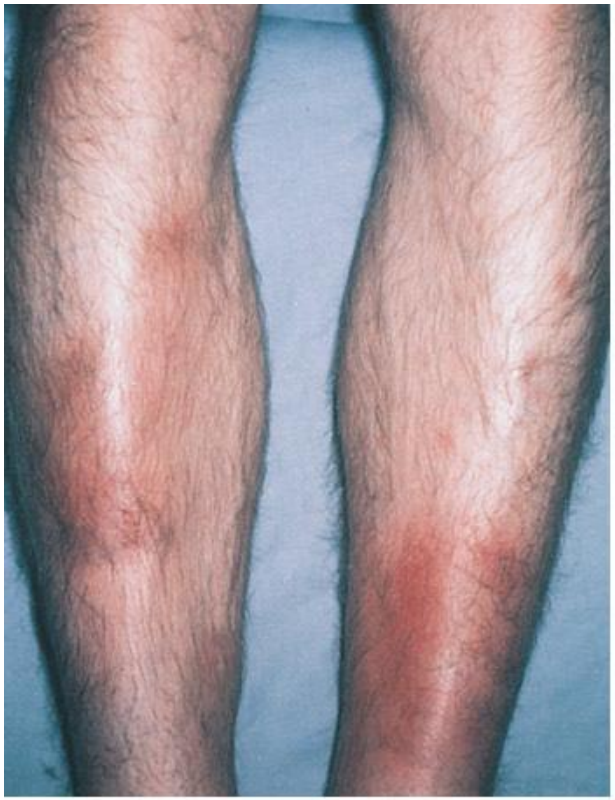
Kawasaki syndrome (febrile systemic vasculitis)

(80 % <5 years old, mostly < 2 years)

cervical lymphadenopathy, polymorphous exanthem, changes in lips and oral cavity, reddening of palms and soles, indurative edema, later membranous desquamation,

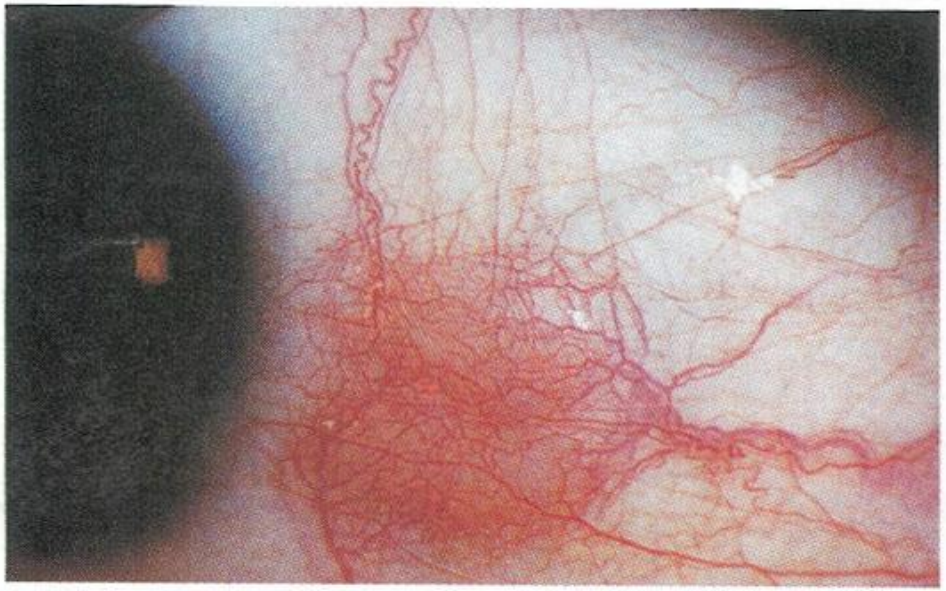
25 % coronary aneurysm, mortality 0,5 – 2,8 %

Sarcoidosis
Erythema nodosum

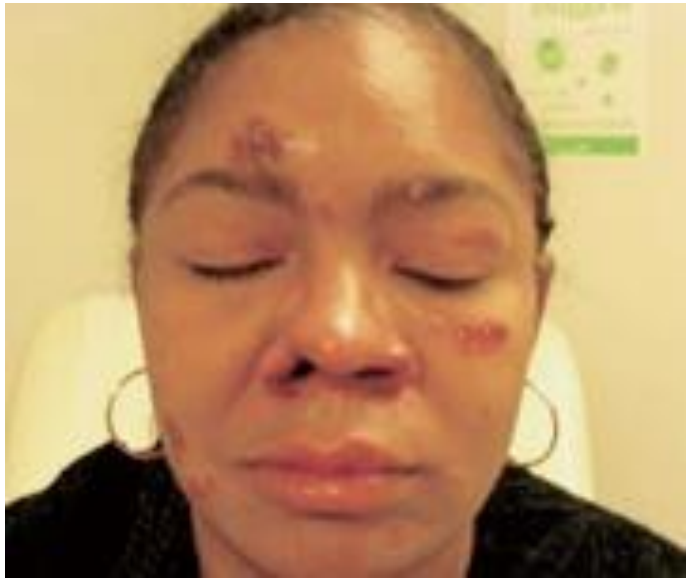


Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo J: *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com

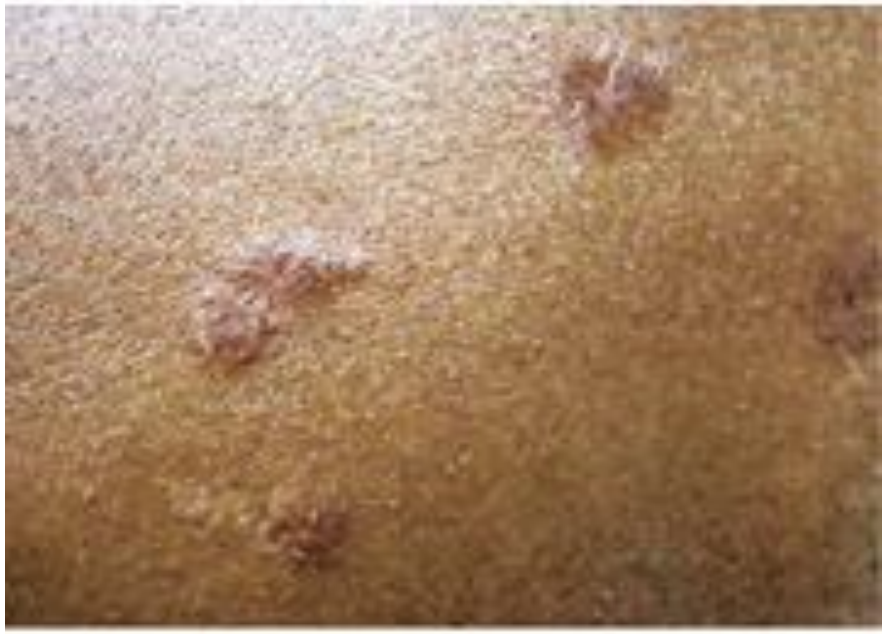
Sarcoidosis
Episcleritis



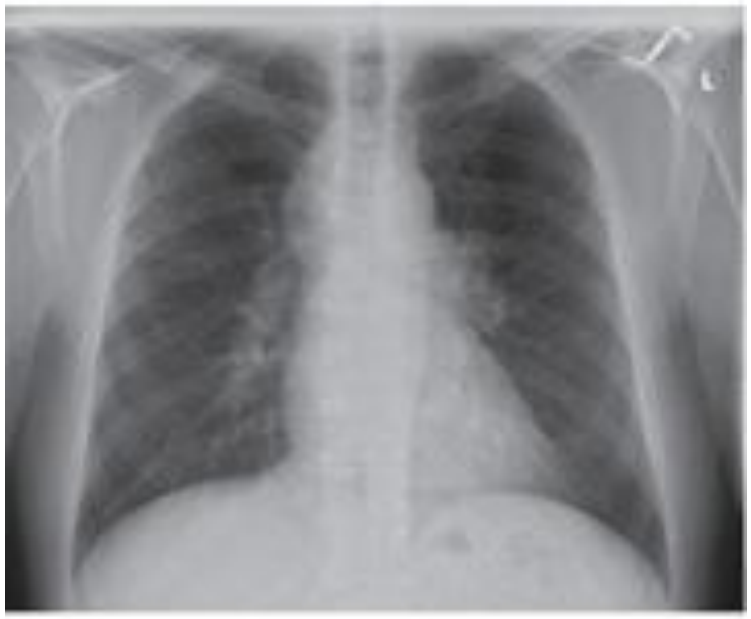
Sarcoidosis



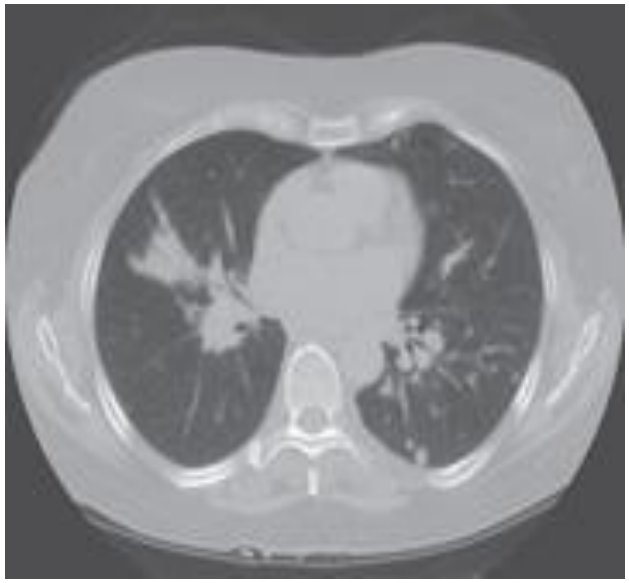
Sarcoidosis



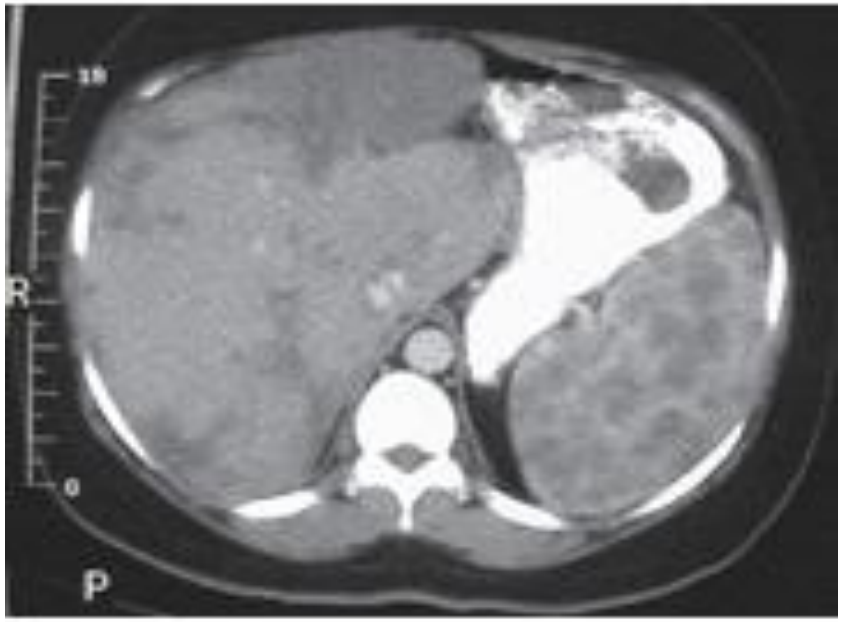
Sarcoidosis (stage I)



Sarcoidosis (stage II)



Sarcoidosis



LYMPHADENOPATHY IN DISORDERS WITH UNKNOWN ETIOLOGY

Castelman's disease: angiofollicular lymph node hyperplasia, young adults

localized lymphadenopathy or mediastinal lymphomas

Langerhans cell histiocytosis: rare clonal neoplastic proliferation of langerhans type cells (that express CD1a), hepatosplenomegaly and lymphadenopathy, bone (eosinophilic granuloma) and adjacent soft tissue

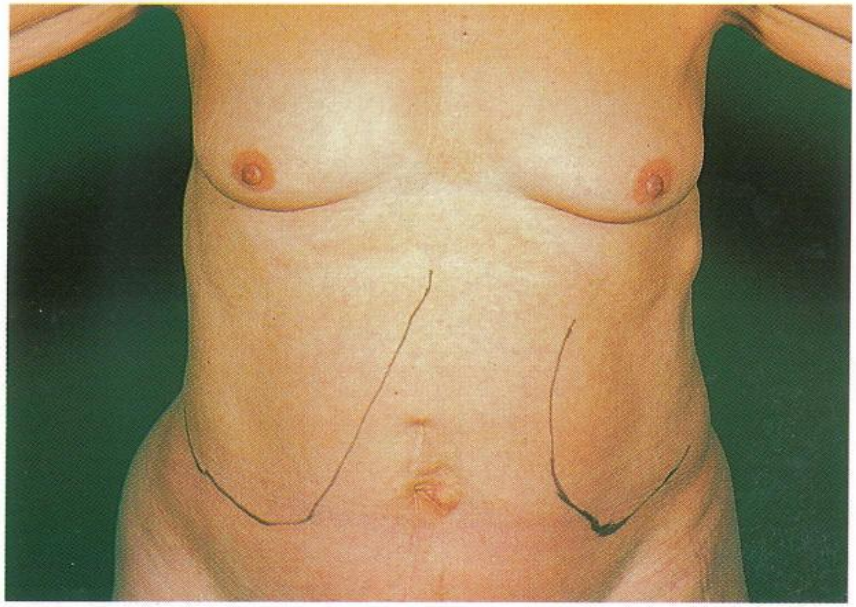
lysosomal storage disease:

Niemann-Pick disease: Sphingomyelin

Gaucher disease: Glucosylceramid

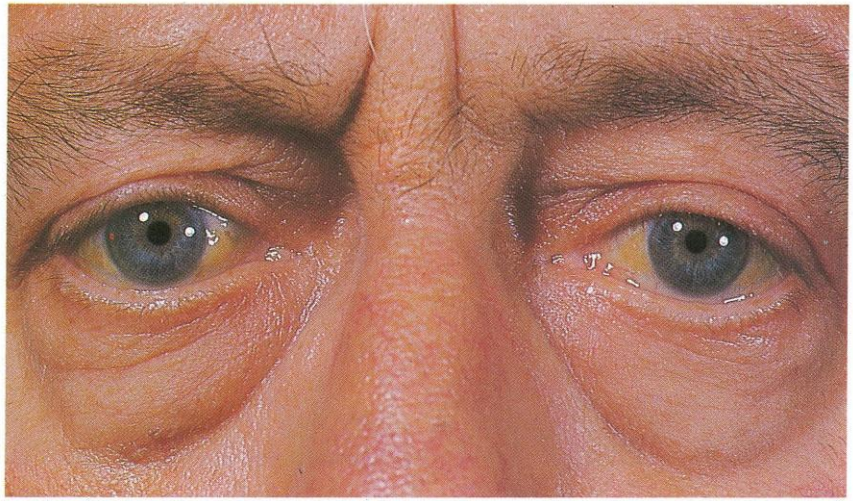
Amyloidosis

lysosomal storage disease
Gaucher disease

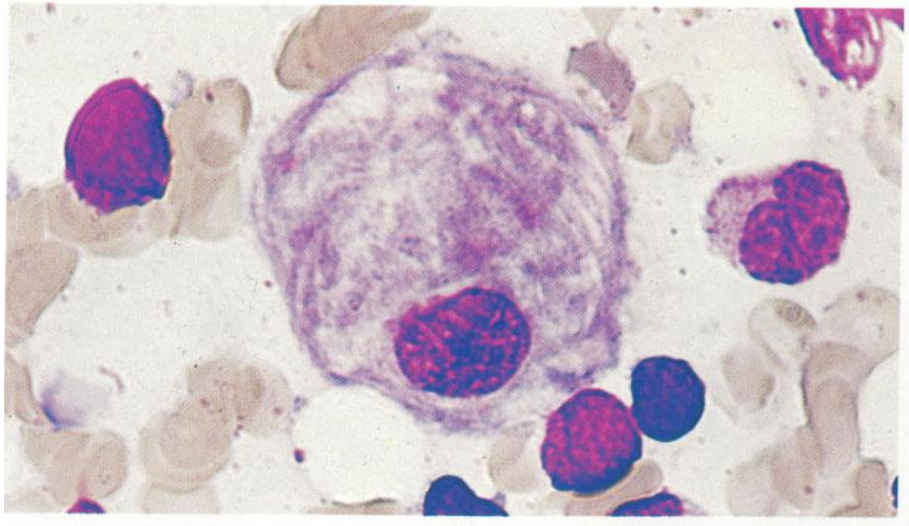


lysosomal storage disease

Gaucher disease (pinguecula, smal yellow growths near the edge of the cornea)



lysosomal storage disease
Gaucher cells



lysosomal storage disease
Niemann-Pick disease

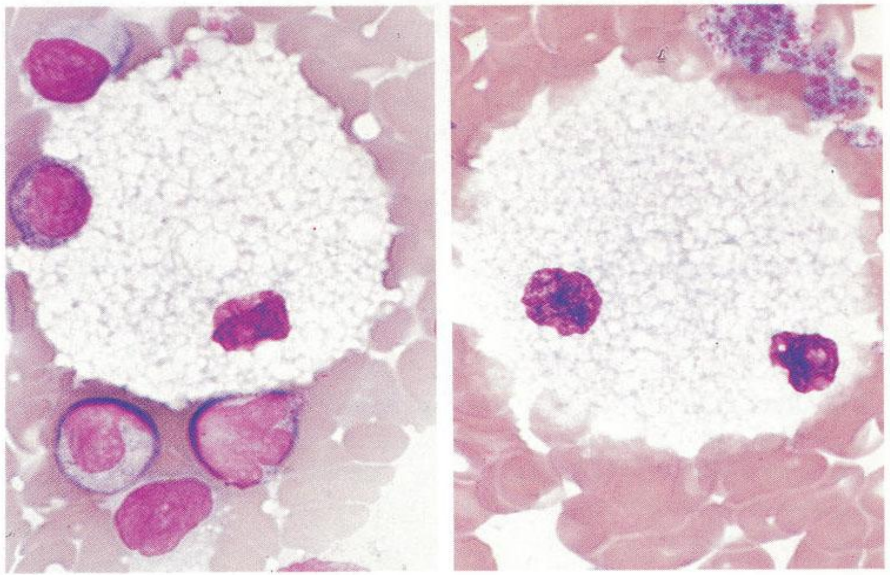
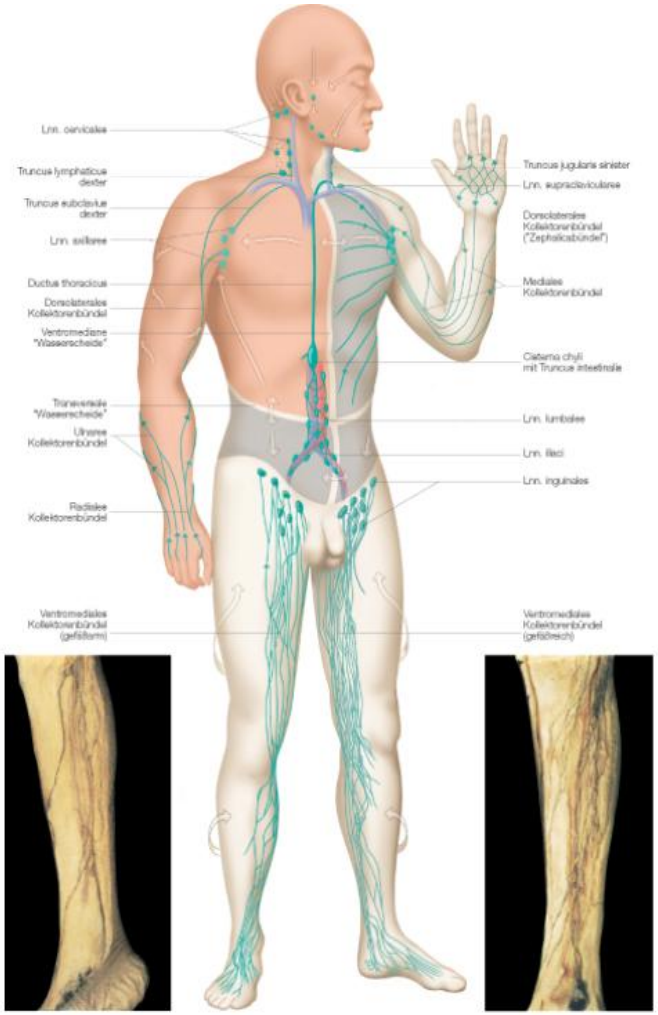


Abb. 15.32
Morbus Niemann-Pick: Histiozyten im Knochenmark mit schaumig aufgelockertem Zytoplasma infolge ausgeprägter Lipidspeicherung.



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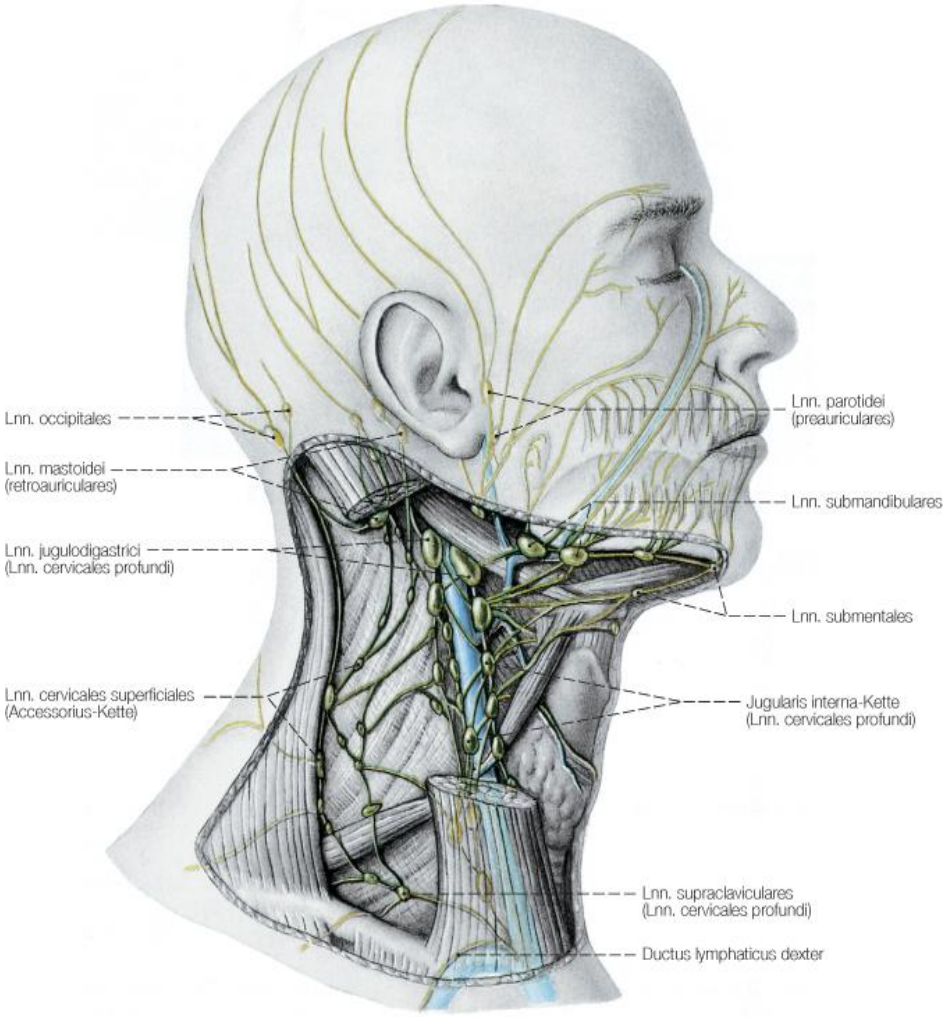
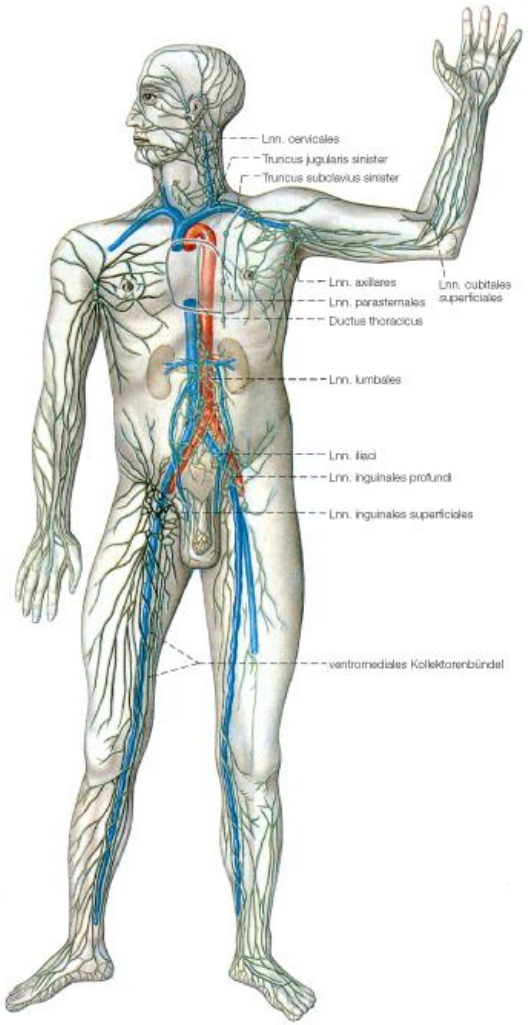
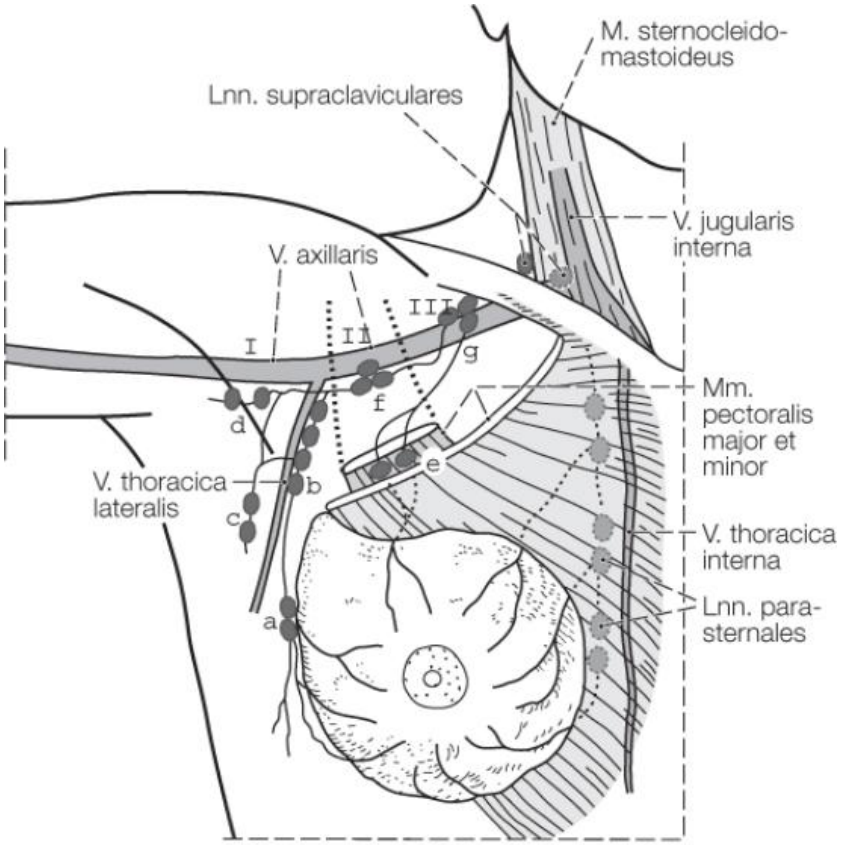
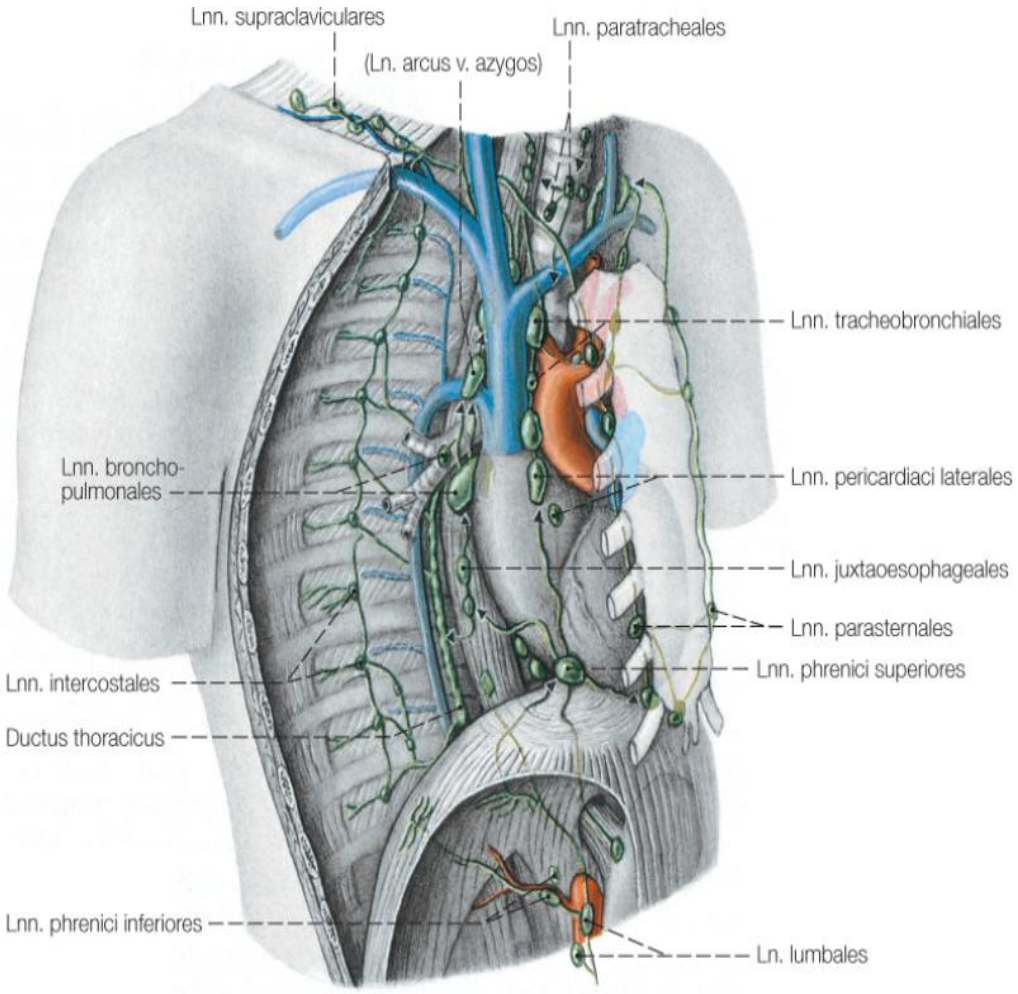






I – III Stockwerke (engl.: levels) der Axilla

I	a	Lnn. paramammarii	II	e Lnn. interpectorales
	b	Lnn. axillares pectorales		f Lnn. axillares centrales
	c	Lnn. axillares subscapulares		
	d	Lnn. axillares laterales	III	g Lnn. axillares apicales



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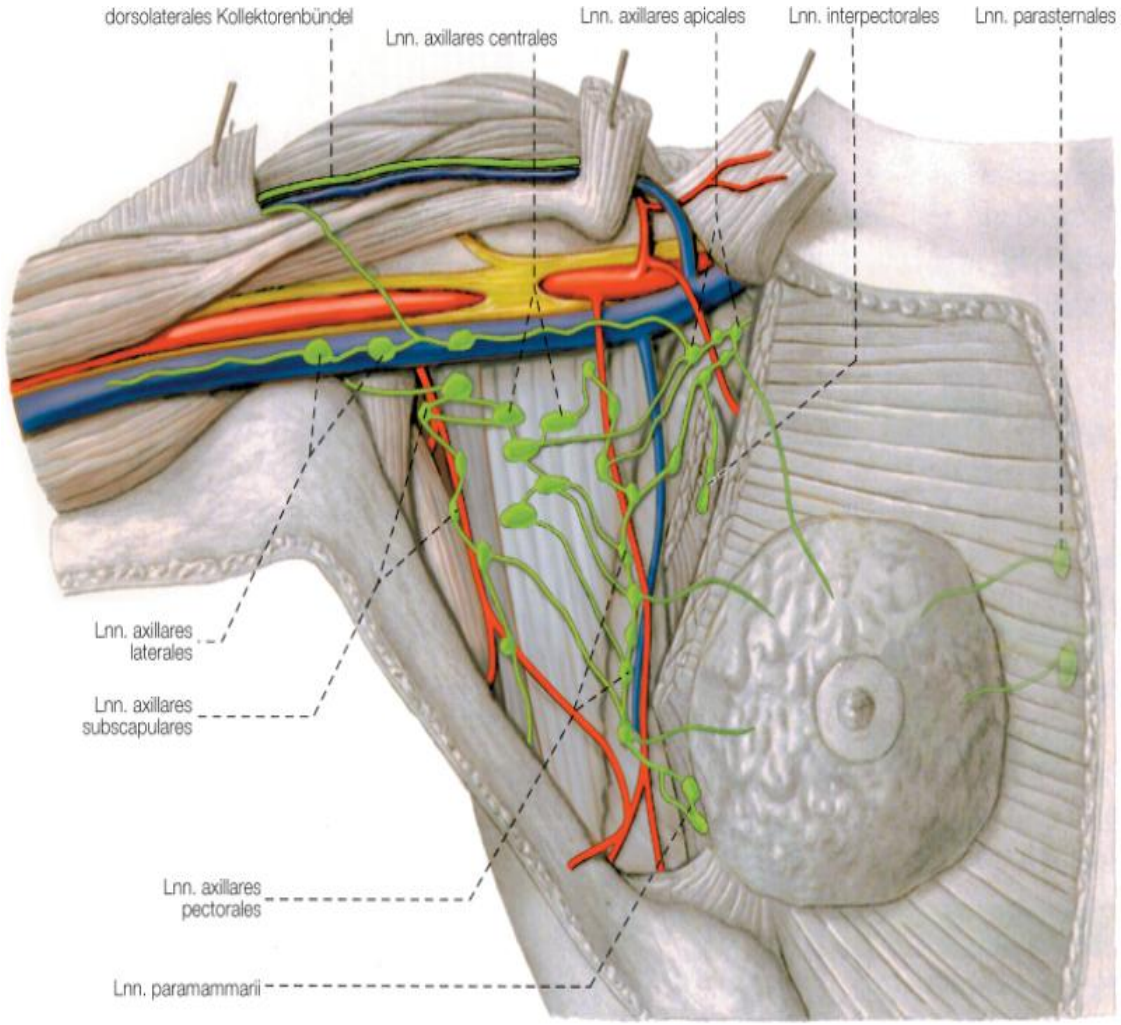

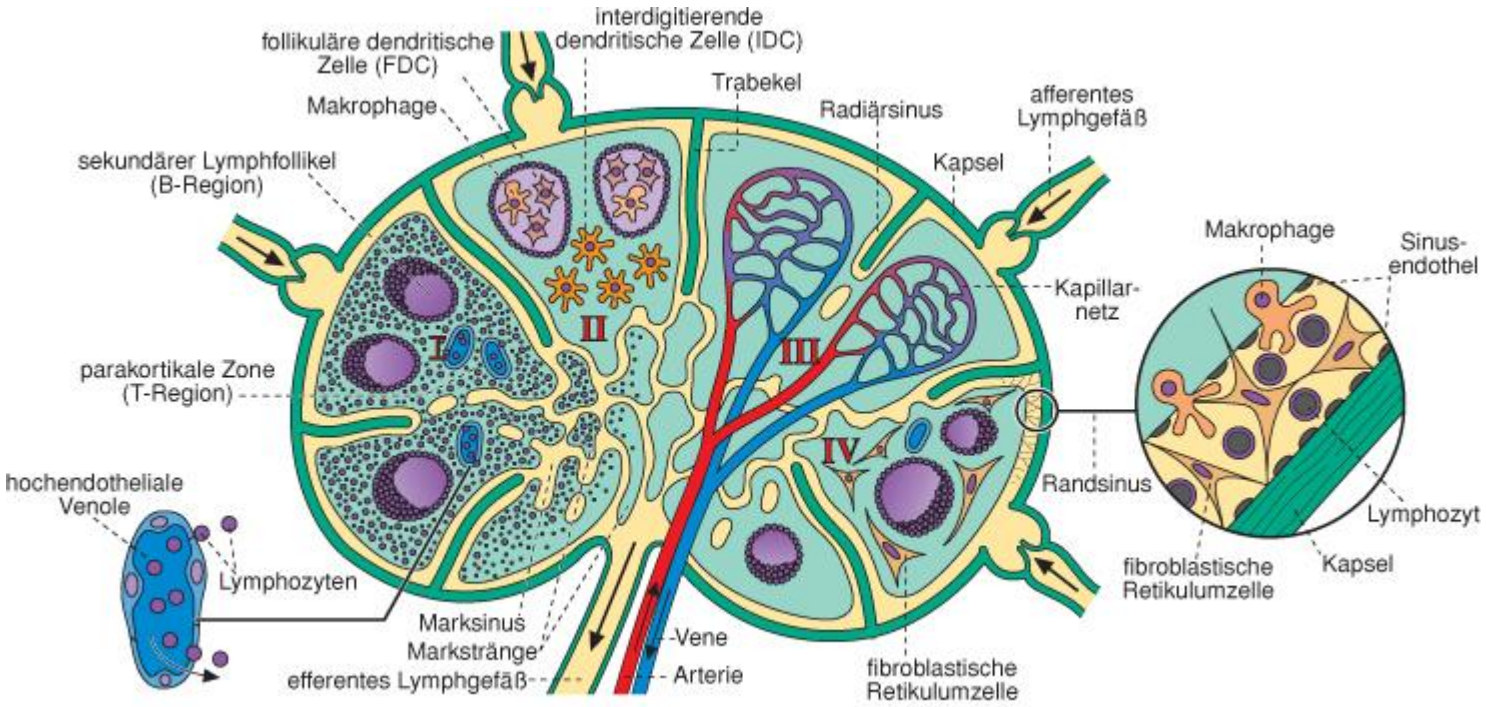

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