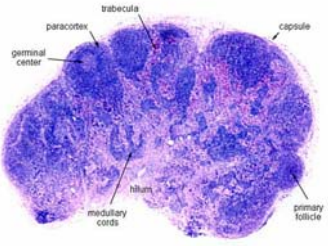
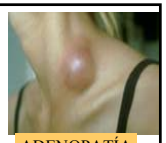
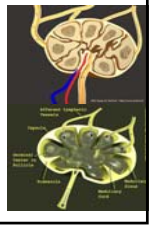
Estructura del ganglio

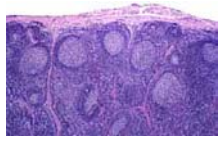


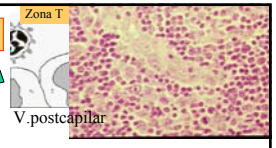


ADENOPATÍA



Cortex y Paracortex





CC

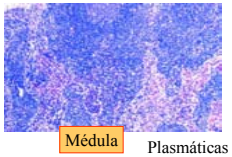
Zona marginal

Zooning del CF

CB

Prime-B

Linfos B



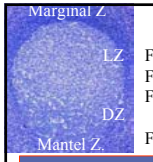
Médula

Plasmáticas

Células Man q

Naïve-B

2



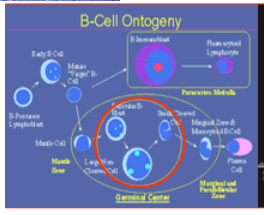
Desarrollo del CF

Fase I- CB

Fase II- CB+cielo estrellado

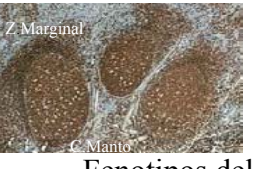
Fase III- Zooning int-densa = CB
ext-clara = cc

Fase IV- cc



3

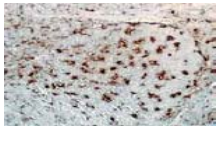
CD20 Pan B



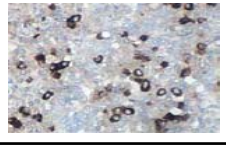
Pan-T

Fenotipos del Centro Folicular

CD68 histiocitos

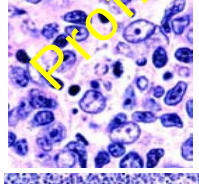


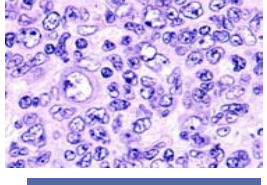
Anti-kappa

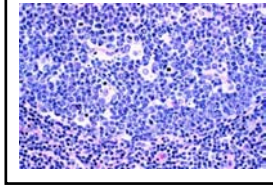


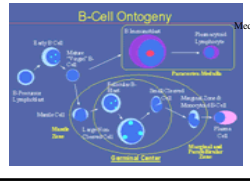
P.V.Corta-IgM

Células del centro folicular

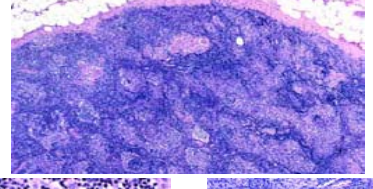


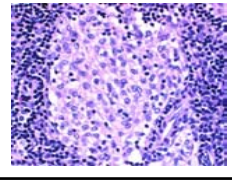


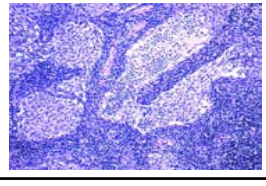




Histiocitosis sinusal







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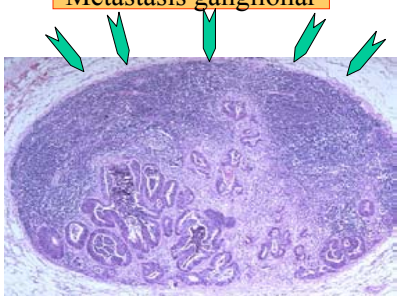
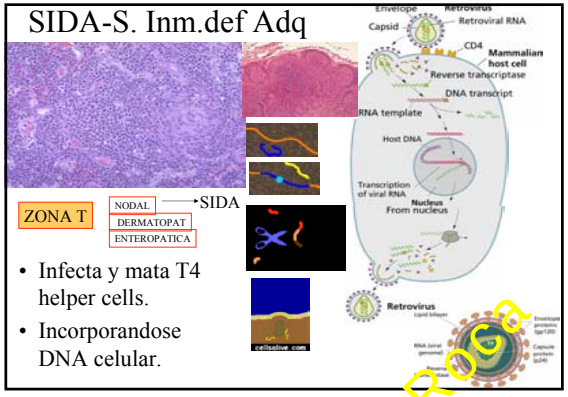
Metástasis ganglionar



SIDA-S. Inm.def Adq

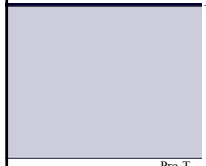


ZONA T

NODAL
DERMATOPAT
ENTEROPATICA
→ SIDA

- Infecta y mata T4 helper cells.
- Incorporandose DNA celular.

Diferenciación embriológic



Tej. Hematopoyéticos embrionarios

Saco Yolk 1º
Hígado 2º
Médula 3º

migran

Pro-T
TdT
TIMO

HIGADO
M.OSEA
T.LINFOEPIT

DNT → CD4 y CD8(-) → **NK**

TCRδ Non-self reacT: **ProT- ALL**

MATURE NAIVE T

DPT → SPT: CD4 y CD8(+)

LINFOS no-T (30%)

circulantes

LINFOS T (70%)	**NULL(NC) (10%)**	**LINFOS B (20%)**
CD4(H) o CD8(S+citotox)	CD3,CD57(+)	Inmun. humoral
Fosfat y esterasa acida +focal	CD16,CD56(+)	

Linfomas No Hodgkin- LNH

NHL

Los linfomas no-Hodgkin son células malignas tipo:

- Linfocitos **B-Cell** el 85% de los linfomas conocidos
- Linfocitos **T-Cell**
- Linfocitos **Unknown NC-NK** **(non-commited/natural killers).**

B-Cells sufren múltiples cambios en su ciclo celular por un **complejo proceso de señalización** al interaccionar con sustancias extrañas al cuerpo.

B-Maduración Centro Reactivo

circulantes

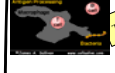
Pre C Germ	**1.Maduros Naive** CD5(+) IgM(++) IgD(++)	*Sin mutación somática*	
	1.1 CD23(-) 1.2 CD23(+) 90%	c.manto	MCL
	+Ag	circulan	B-CLL
	Prime B extrafolic IgM(+++)	c.plasm v corta	LPL IC WD
	+Ag		
C.Germinal	**2. Prime B** **CD20 +**	*Mutación somática Ig*	
Post C Germ	**3. B de Memoria** CD5,23,10(-) IgM(+++)IgD(+/-)	*Ig± somat no activa*	
	3.1 en el margen 3.2 mucosas	c. zona marginal	MZL
	+Ag	bazo/intest	LMAL
		c.plasm v larga	M IB

NHL

circulantes

Cambios en los CR.

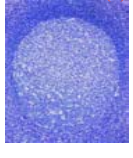
FDC= C.Folicular dendrítica CD21(+)
- capturan los Ag-Ac Plasmat Vc
- lo presentan a las cel B-naïve



T4-MCHII

3.1 Sale memory B
3.2 Apoptosis BCL2(-)
3.3 Plasmat. V larga

CD10/CALLA(+)



LZ Light zone	3	cc	
DZ Dark zone	2	CB	
	1	Pre-CB	

M Osea M
Intestino IBL
Lcc
BCL2(+)
Lcc CB
LCB
LB Burkitt

NHL

Entran en el CR por el polo inferior

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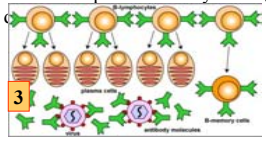
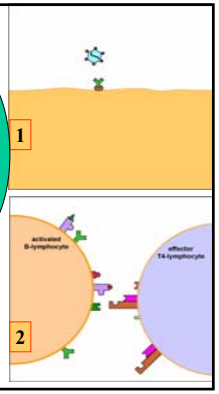
Células B

1. Unión epitópos(Ag-recp B) y producción de MCH-II
2. T4 Helpers (CD28-CD4) reconocen los MCH-II + unión CD40 →activan linfos B.
3. →Inicia la proliferación y





NHL Etiología de los linfomas B
Ch14-IGH

❑La mayoría de los **linfomas foliculares** → **Ch14**

➢La mayoría de los linfomas del manto (**MCL**) tiene un reajuste en el **gen BCL-1 en 11** que codifica la **ciclina D1 reguladora de la fase G1 ciclo celular, t(11;14)** →**obligarian a entrar en el CR.**

➢La mayoría de los linfomas Linfomas linfoblásticos (**Llb**) incluido el Burkitt tiene una translocación entre **gen MYC en 8 y el de la IGH el locus de la cadena pesada de la Ig en 14, t(8;14).**

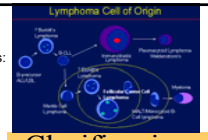
➢Los linfomas centrocíticos (**Lcc**) tienen una translocación entre el gen **BCL-2** y el de la producción de la IGH **t(14;18)** → **sobre-expresión del gen BCL-2.**

El BCL-2 ordena la producción de una proteina de la membrana interna mitocondrial que bloquea la muerte programada de la célula (apoptosis).

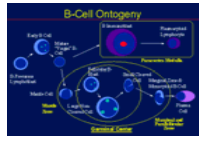
14

Linfomas-B, segun las celulas B afectas:

- Follicular lymphomas are divided into 3 types according to the ratio of small-cleaved and large cells:
  1. Small-cleaved cell type
  2. Mixed small-cleaved and large cell type
  3. Large cell type
- Small Non-Cleaved Cell Lymphomas
  1. Endemic Burkitt's lymphoma
  2. Sporadic Burkitt's lymphoma
  3. Adquired Burkitt's+ AIDS
  4. Non-Burkitt's lymphoma
- Marginal Zone Lymphoma
  1. Mucosa-Associated Lymphoid Tissue MALT / MALToma (extranodal)
  2. Monocytoid B-cell lymphoma (nodal)
  3. Splenic Lymphoma with villous lymphocytes
- Mantle Cell Lymphoma
- Large Cell Lymphoma
  1. Diffuse Large Cell
  2. Diffuse Mixed Cell
  3. Immunoblastic Lymphoma
  4. Primary Mediastinal B-Cell Lymphoma
  5. Angiocentric Lymphoma - Pulmonary B-Cell
- Small Lymphocytic Lymphoma



Clasificacion Linfoma B

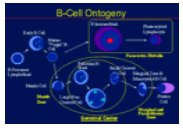


Clasificación REAL linfoma B

Precursor B-cell neoplasm: precursor B-lymphoblastic leukemia/lymphoma

Peripheral B-cell neoplasms.

A. B-cell chronic lymphocytic leukemia/prolymphocytic leukemia/small lymphocytic lymphoma
B. Lymphoplasmacytoid lymphoma/immunocytoma
C. Mantle cell lymphoma
D. Follicle center cell lymphoma, follicular
   1. Provisional cytologic grades:
      I small cell,
      II mixed small and large cell,
      III large cell
   2. Provisional subtype: diffuse, predominantly small cell type
E. Marginal zone B-cell lymphoma
   1. Extranodal (MALT-type +/- monocytoid B cells)
   2. Nodal (+/- monocytoid B cells)
F. Provisional entity: splenic marginal zone lymphoma (+/- villous lymphocytes)
G. Hairy cell leukemia
H. Plasmacytoma/plasma cell myeloma
I. Diffuse large B-cell lymphoma
   1. Subtype: primary mediastinal (thymic) B-cell lymphoma
J. Burkitt's lymphoma
K. Provisional entity: high-grade B-cell lymphoma, Burkitt-like



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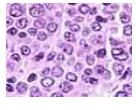
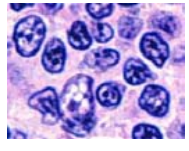
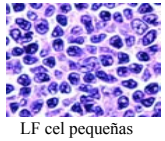
NHL

Linfomas Nodulares BCL2 +

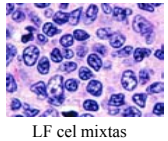
Lcc-CB



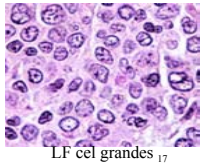




LF cel pequeñas



LF cel mixtas

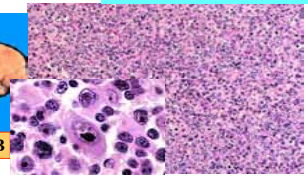


LF cel grandes 17

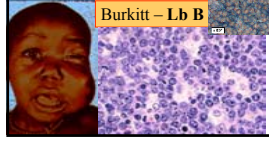
NHL

Linfomas difusos

Linfoma inmunoblastico IB

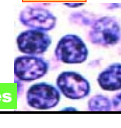


CD20 +



Burkitt – Lb B

B-CLL



circulantes

Prof. Dr. O. Ferrer-Roca

Estadíos Clínicos

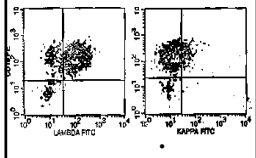
LINFOMAS NO CIRCULANTES …..... **Ann Arbor**
RUTAS METASTASICA…. Según su recirculac normal

1. INVASION LOCAL E I
2. INVASION LINFATICA E II
3. diafragma E III
4. INVASION HEMATOGENA E IV
   Hígado/ MedOsea

LINFOMAS CIRCULANTES …….. **RAI (leucemias)**
E0…. + 15000 leucos periféricos/ +40% linfos Med.Osea
EI …. Idem + adenopatías
EII… Idem + Hepato-esplenomegalia
EIII.. Idem + Anemia
EIV.. Idem + Plaquetopenia (-100000 plaquetas)

19

Fenotipos Linfoides



TERAPIA-Rituximab
•**anti-CD20 quimérico** → destruye **LNH bajo grado o foliculares**.

•Se fija a las células presentadoras de antígenos o a los histiocitos que fagocitan las cel. linfoides.

DIAGNOSTICO

•**Todas las cel.linfoides** (casi todas): **CD45-LCA** (antigeno leucocitario comun).

•**B-cells**: (casi todas) CD19, **CD20** y CD22. Algunos linfomas de bajo grado son + a ag.propios de las celulas T: CD5 y CD43. Linfomas foliculares con frecuencia son **CD10**(+).

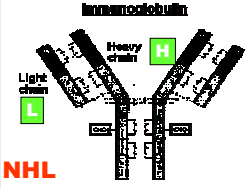
•**T-cells**: Pan-T (casi todas) CD2, CD3, CD5, y CD7.
•La mayoria cel. T son o bien CD4 (helper) or CD8 (suppressor or cytotoxic).

•**Natural-killer cells**: Son con frecuencia CD16, **CD56**, or **CD57**.

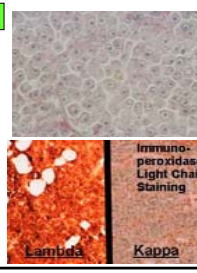
20

Cel. secretoras monoclonales

- **IB LIB**
- **P** - Vcorta: **LPL**, **WM**, **IC** **H-IgM**
- - Vlarga: **MM** **L**



NHL

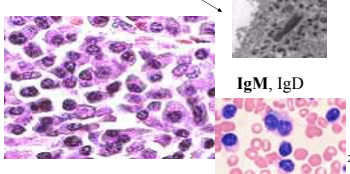


NHL

WD - Enf. Waldenstrom

Aspectos que la hacen maligna (con excepciones)
- Proteína-M (macroglobulinemia - IgM) > 3 g/dl
- Cel. Plasmáticas > 10% celularidad de la M.Ósea
- Marcaje elevado en plasmáticas (proliferativa)
- Es monoclonal con frecuencia κ → BJP

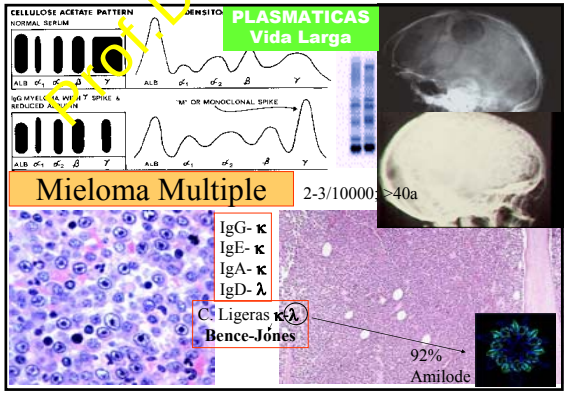
IgM pentámero



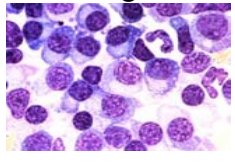
PLASMATICAS Vida Corta

IgM, IgD

22



Inmuno-fenotipo CP malignas



- **Igual que las CP** benignas son:
  1) Negativas
     - CD19 y CD20 propio de cel B maduras y al
     - LCA- CD45, antígeno pan-leucocitario.
  2) Positivas
     - **CD38**, plasma cell antigen-1 y con frecuencia EMA
- **A diferencia** de las CP benignas son.
  3) Positivas
     - **CD56**, molecula de adhesion neuronal.

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Diferenciación embriológica

Tej.Hematopoyéticos embrionarios

Saco Yolk 1º
Hígado 2º
Médula 3º

migran

Pro-T
TdT
TIMO

HIGADO
M.OSEA
T.LINFOEPIT

DNT → CD4 y CD8(-) → NK
TCRδ Non-self reacT: ProT- ALL
MATURE NAÏVE T
DPT → SPT: CD4 y CD8(+)

LINFOS no-T (30%)

circulantes | LINFOS T (70%) CD4(H) o CD8(S+citotox) Fosfat y esterasa acida +focal | NK-NULL(NC) (10%) CD3,CD57(+) CD16,CD56(+) | LINFOS B (20%) Inmun. humoral

25

Th1 citoquinas , Tc, NK cells

Tc / NK

Cel. Interdigitada dendrítica — INMUNIDAD CELULAR — Th1

Mediada macrófagos

MCH-I

MCH-II

CD4-helper Th- MCH-II
CD8-supresor Tc- MCH-I
CD8-CD4 (-) NK-MCH-I

Cytotoxic T-Lymphocyte Killing Target
© James A. Sullivan Quill Graphics Charlottesville, VA USA

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Desarrollo cel T

circulantes

Pre ZPV 1. Maduros Naive CD4(+) Helper CD8(+)Supres — Sin mut. somática — T- CLL

+ Ag

Z.Periven 2. Prime T Blasto T CD30 + — Mutación somática — Angioinmunob. AILD — Linfoma T anap ALCL

Post ZPV 3. T de Memoria — Mutac.sem.no activa

3.1 Solo Organos
3.1.1.T-Mucosas MLA/CD103(+) — Enteropatia T ETCL
3.1.2 T-Cutaneos CLA(+) — Micosis Fung MF — S. Sezary SZ
3.1.3 T-Nodales

NHL

3.2 No restringido organ T+NK — Leuc.L.granular LGLL — L.nasal angioc. AI

circulantes

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Clasificación de los linfomas T

T-cell and putative NK-cell neoplasms
I. Precursor T-cell neoplasm: precursor T-lymphoblastic lymphoma/leukemia ALL-T
II. Peripheral T-cell and NK-cell neoplasms
A. T-cell chronic lymphocytic leukemia / prolymphocytic leukemia
B. Large granular lymphocyte leukemia 1. T-cell type 2. NK-cell type
C. Mycosis fungoides/Sezary's syndrome
D. Peripheral T-cell lymphomas, unspecified
1.Provisional cytologic categories: medium-sized cell, mixed medium and large cell, large cell, lymphoepithelioid cell
2.Provisional subtype: hepatosplenic gamma/delta T-cell lymphoma
3.Provisional subtype: subcutaneous panniculitic T-cell lymphoma
E. Angioimmunoblastic T-cell lymphoma
F. Angiocentric lymphoma
G. Intestinal T-cell lymphoma (+/- enteropathy associated)
H. Adult T-cell lymphoma/leukemia
I. Anaplastic large cell lymphoma
1. CD30+ -cell type – Ki-1
2. T-cell type
3. Null-cell types
J. Provisional entity: anaplastic large cell lymphoma, Hodgkin's-like

CD30 +

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Clasificación linfomas T

Linfomas T-Cell según la célula T afecta
- Linfomas linfoblásticos (precursores) T LLB-T
- Linfoma T cel. grandes anaplásico CD30 + (ALCL)
- Linfoma **Angio**inmunoblastico.
- Linfomas T **cutáneos**: Micosis Fungoide / Sind. Sezary
- Linfomas NK/T perifericos (PTCL): Linfoepit; hepatoesplen; subcutaneos.(10% NHL)
  - Linfoma **Angio**centrico (Linfoma nasal de cel T)
  - Linfoma T **intestinal**.
- Linfoma cel T adultas LLT(leucemia linfatica T)

Linfoma T hepat-espln

NK-CD56

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Linfoma Linfoblástico — NHL — Small non-cleaved

T — A-LL — B — Burkitt

Stem cells o precursores - LLb

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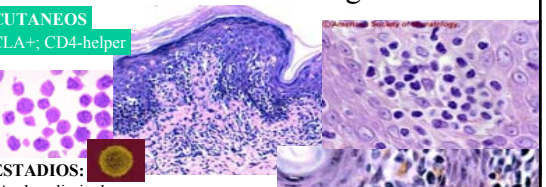
NHL

CUTANEOS:Micosis Fungoide MF/SS

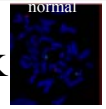
CUTANEOS
CLA+; CD4-helper



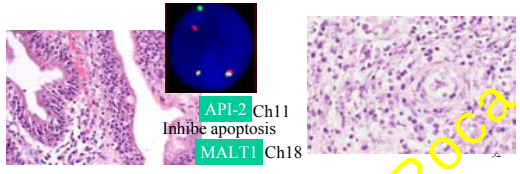
ESTADIOS:
IA-placa limitada
IIA-IB- placa extensa
IB-tumor
IIIA-Eritrodermia sin Sezary
IIIB-Eritrodermia con Sezary (T sangre)
IV- Afectación ganglionar o visceral.

NHL

MUCOSAS: T-Malt / NK



- Nasal angiocéntrico T/NK (no-ALCL) CD4/CD56
- Linfoepiteliales EBV +/-
- T intestinales con o sin enteropatía MCLA **t(11**q22**:18**q21**)**



Linfoma T cel grandes anaplásicas-ALCL

NHL

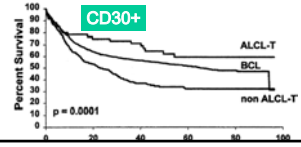
ETIOLOGIA

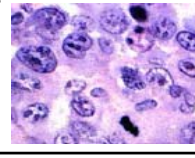
•Linfomas anaplásicos de células grandes ("clásico", que afecta a adolescentes y niños y afecta a la piel)
•Tiene una translocación **t(2;5)**
2p23 ALK=Anaplasic lymphoma kinasa y 5q35 NPM= Nucleofosmina formando la proteína quimérica p80.

CD45+

•Tipos: Ki-1 (CD30+); NC=null cells; T-cells

CD30+





Etiología Linfomas T
TCR-TcellReceptor Rearrangement

anomalía Cr mas frecuente en **LLb-T** es recombinaciones en *TCR alfa-delta* **14q11** y los genes *TCR beta(7)*, y *gamma(7)*, ademas los Cr **9**, **10**, and **11**.

Function	Protein Product	Ch Aberration	Involved Genes
Transcp fact	Basic HLH proteins	t(1;14)(p32-34;q11)	*TAL1-TCR*alphadelta
		t(1;7)(p32;q35)	*TAL1-TCR*beta
		t(7;9)(q34;q32)	*TAL2-TCR*beta
		t(7;19)(q35;p13)	*LYL1-TCR*beta
		t(8;14)(q24;q11)	*MYC-TCR*alphadelta
	Homeodomain proteins	t(10;14)(q24;q11)	*HOX11-TCR*alphadelta
	LIM domain proteins	t(11;14)(p15q11)	*RHOM1-TCR*alphadelta
		t(11;14)(p13q11)	*RHOM2-TCR*alphadelta
	Fusion proteins	t(1;19)(q23;p13)	*PBX1-E2A*
		t(10;11)(p13;q14)	*AF10-CALM*
Signal transduction	Protein kinase	t(1;7)(p34;q34)	*LCK-TCR*beta
	Notch homologue	t(7;9)(q34;p34)	*TAN1-TCR*beta
Cyclin-dependent	$p16^{INK4A}$ /$p15^{INK4B}$	del(9)(p21-22)	*MST1/MST2*
Unknown	Unknown Ig	inv(14)(q11;q32.1)	*TCL1-TCR*alphadelta[4]
		t(14;14)(q11;q32.1)	*IgH-TCR*alphadelta

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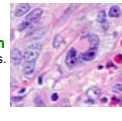
Como se diagnostica un LNH?

- 1- Borramiento estructura ganglionar
- 2.- Nodular o difuso?
- 3.- Patrón cielo estrellado? Alto o bajo grado?

HODGKIN

•1966 Rye Classification→cHL.

Hodgkin's Disease-HD /HL REAL Classification
Classical Hodgkin Lymphoma cHL (95%) with T markers.
I. LR- Lymphocyte rich
II. NS- Nodular sclerosis
III. MC- Mixed cellularity
IV. LD- Lymphocyte depletion
Nodular lymphocyte predominant NLPHL (5%) a B-cell neoplasm (FC).

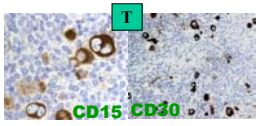


Hodgkin cell is most likely an aberrant B lymphocyte
Schwartz RS. Hodgkin's Disease--Time for a Change. N Engl J Med 1997; 337:495-6).

DG: Células diagnosticas + Cortejo acompañante

Etiología: Inmuno-fenotipo cel R-S

El inmunofenotipo de las células de Reed-Sternberg varia según las variantes histológicas de Hodgkin en forma de espejo:

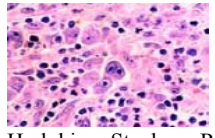


En un 80% de C.mixta y 35% EN las cel. R-S contienen virus EB.
A mas virus → peor pronóstico.

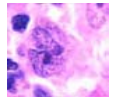
	CD15	CD30 Ki-1	LCA-CD45 (all leukocytes)	CD20 (B-cells)	EMA
LHodgkin clasico cHL	+	+	-	-	-
LHN Predominio linfoc.	-	-	+	+	+

Células diagnosticas LH

Célula lacunar
cHL Esclerosis nodular



Célula L & H ,
pop-corn del HL Predominio linfocitico



Cel Hodgkin y Stenberg-Reed
cHL, sobretodo cel mixta

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LH. Nod. Predominio Linfocítico

L&H=Lymphocytic & Histiocytic
5%

M/F= 4/1

CD45 CD20

Rituximab

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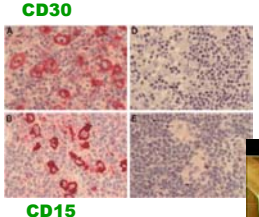
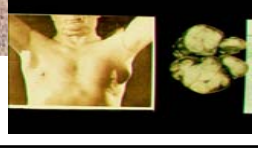
cLH. Rico en Linfocitos

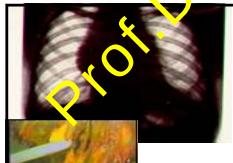


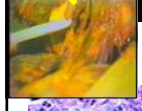
5%

Edad media = 35 años
M/F= 1.5:1

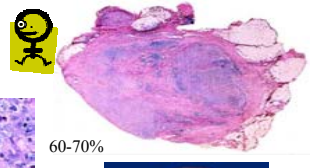


Single lymph node

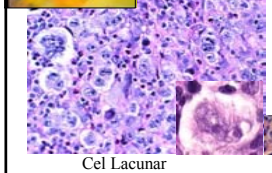


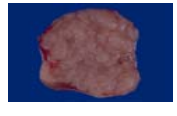


LHc. Esclerosis Nodular



60-70%



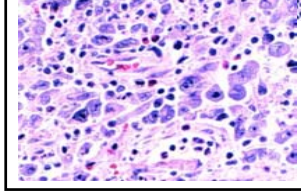


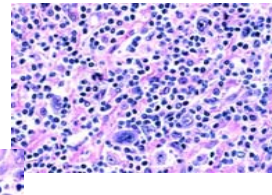
Cel Lacunar

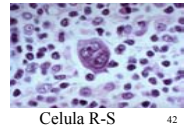
41

H.Celularidad Mixta

20-30%







Celula R-S

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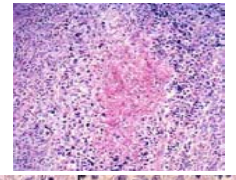
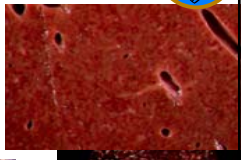
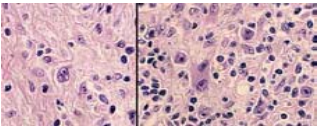
H.Deplección Linfocitica – 50a

5%

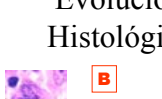






Bazo Porfidø[3]

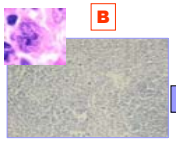
Evolución Histológica



B

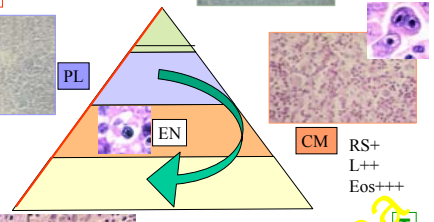
LR

R-S – L++++



PL

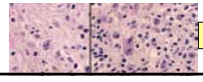
R-S +/- L+++



EN

CM

RS+ L++ Eos+++



DL

R-S +++, anómalas L -

T

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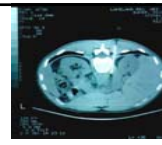
Clasificación de Ann Arbor



Stage I
Involvement of a single lymph node or extra-lymphatic site (IE)

Stage II
Involvement of 2 or more lymph node regions on the same side of the diaphragm or localized involvement of an extra-lymphatic site (IIE)

Stage III
Involvement of lymph node regions on both sides of the diaphragm or localized involvement of an extra-lymphatic organ or site (IIIE) or spleen (IIIS) or both (IIISE)

Stage IV
Diffuse or disseminated involvement of one or more extra-lymphatic organs with o without associated lymph node involvement

The stage can also have a designation of "A" for asymptomatic or "B" for constitutional symptoms.

FIN

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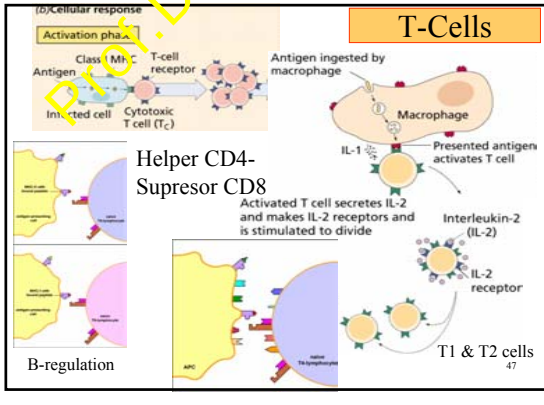
T-Cells



Helper CD4-
Supresor CD8

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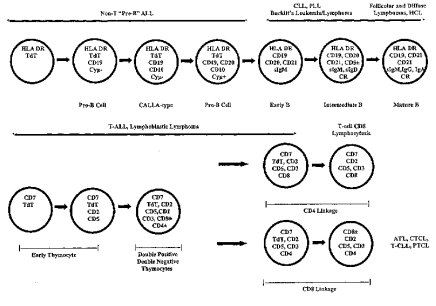
Marcadores linfomas



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