

Microbiopsie ganglionnaire dans les lymphomes B à grandes cellules

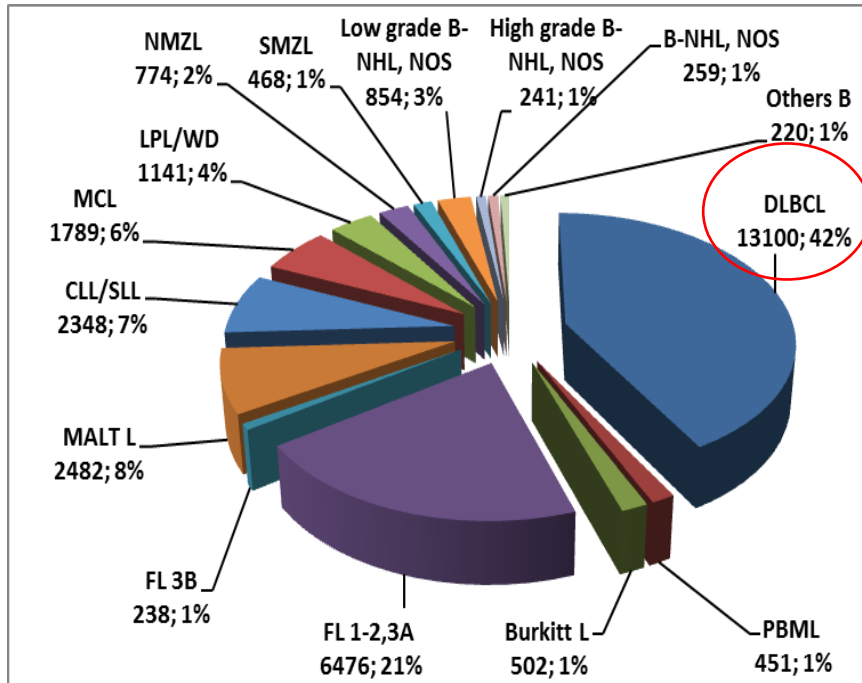
Journée AIP/Carrefour Pathologie - Jeudi 7 novembre 2019-Paris

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Créteil, France

LYMPHOPATH

Lymphomes B à grandes cellules (LBGC)



Distribution of the 32 568 nodal or extranodal mature lymphomas diagnosed over a 2010-2013 period according to the WHO 2008

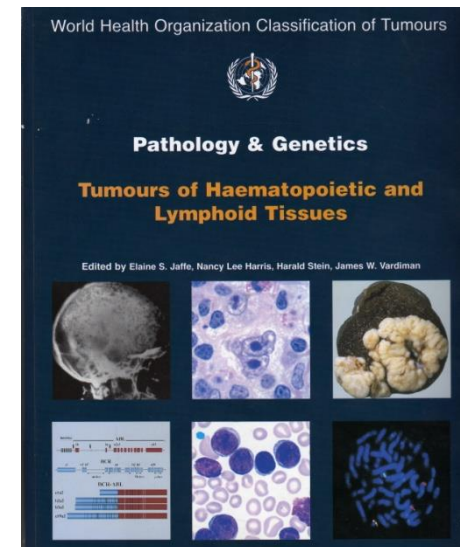
Laurent C, J Clin Oncol 2017

- 30-40 % des lymphomes de l'adulte
- 4 à 5000 nouveaux cas/an en France
- Grande hétérogénéité morphologique, clinique et biologique
- Evolution spontanée «agressive»
- Curable avec une immunochemiothérapie mais 30-40% des patients sont soit réfractaires au traitement ou rechutent.

Les lymphomes B à grandes cellules

- • **Diffuse large B-cell lymphoma (DLBCL) , not otherwise specified (NOS) = 80%**
 - Germinal centre B-cell type*
 - Activated B-cell type*
- T-cell/histiocyte-rich large B-cell lymphoma
- **DLBCL, topographic site related**
 - primary mediastinal (thymic) large B-cell lymphoma (PMBL)
 - primary DLBCL of the CNS
 - primary cutaneous DLBCL, leg-type
 - intravascular large B-cell lymphoma
- **DLBCL, EBV related**
 - EBV-positive DLBCL, NOS*
 - DLBCL associated with chronic inflammation
 - Lymphomatoid granulomatosis
- **LBCL with terminal B-cell differentiation**
 - Plasmablastic lymphomas
 - ALK+ LBCL, Primary effusion lymphoma (PEL)
 - HHV8+ DLBCL, NOS**
- **Burkitt lymphoma (BL)**
 - Burkitt like lymphoma with 11q aberrations**
- • **High-grade B-cell lymphoma (HGBL)**
 - HGBL with MYC and BCL2 and/or BCL6 rearrangements (HGBL-DH)*
 - HGBL, not otherwise specified (NOS)*
- **B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma**

OMS 2016



Les entités provisoires sont listées en italique

**indique le changement de nomenclature par rapport à la classification 2008*

DLBCL NOS: la cellule d'origine

Gene Expression profiling (GEP)

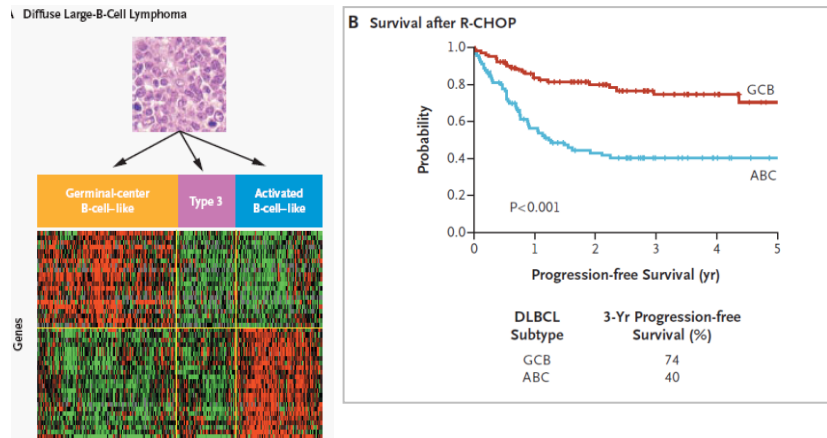
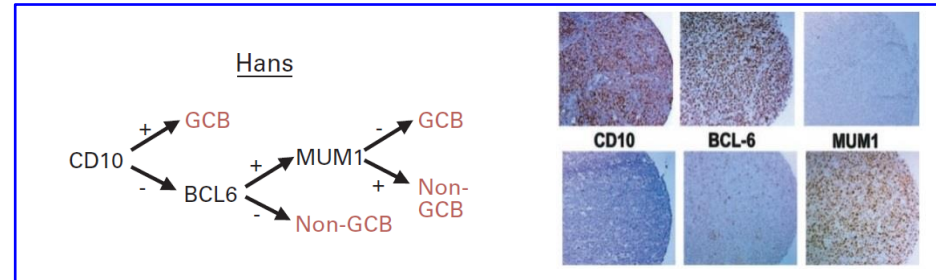


Table 1 | Oncogenic mechanisms and potential targets in DLBCL subtypes

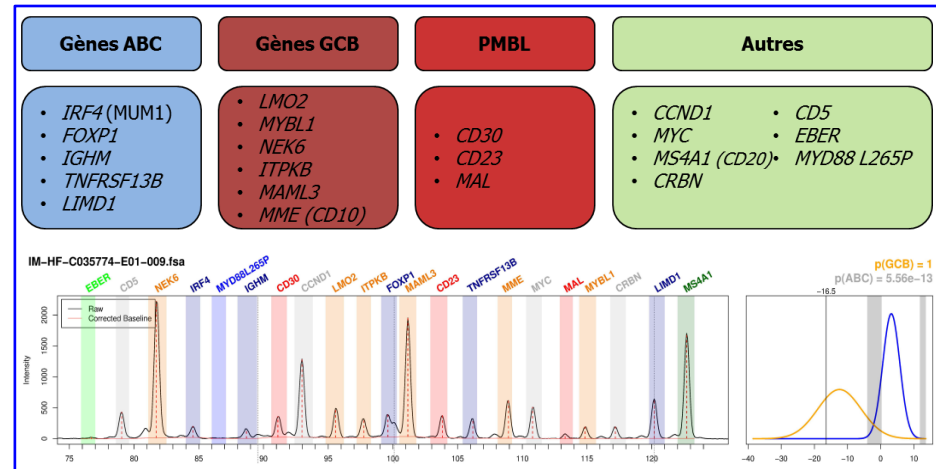
DLBCL subtype	Cell of origin	Oncogenic mechanisms	Potential targets
GCB	Germinal centre B-cell	<i>BCL2</i> translocation* <i>EZH2</i> mutations [‡] <i>PTEN</i> deletions [§] Loss of <i>PTEN</i> expression	<i>BCL6</i> <i>EZH2</i> <i>PI3K/Akt</i>
ABC	Post-germinal centre B-cell	<i>NF-κB</i> activation <i>CARD11</i> mutations <i>MYD88</i> mutations <i>CD79B</i> mutations <i>A20</i> deletions	<i>BCR</i> CBM complex <i>IRAK-4</i> <i>JAK-STAT</i>

Alizadeh et al, Nature 2000, Rosenwald et al NEJM 2002, Rosenwald et al J Exp Med 2003, Review: Roschewski M, Nature Review 2013

Score de Hans (Hans, Blood 2004)

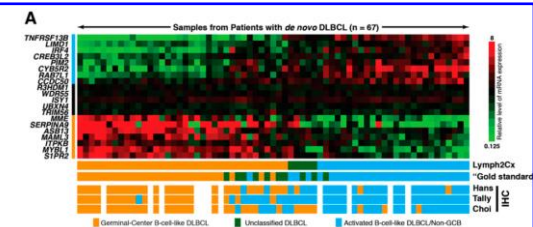


RT-MLPA (Bobee V, J Mol Diag 2017)



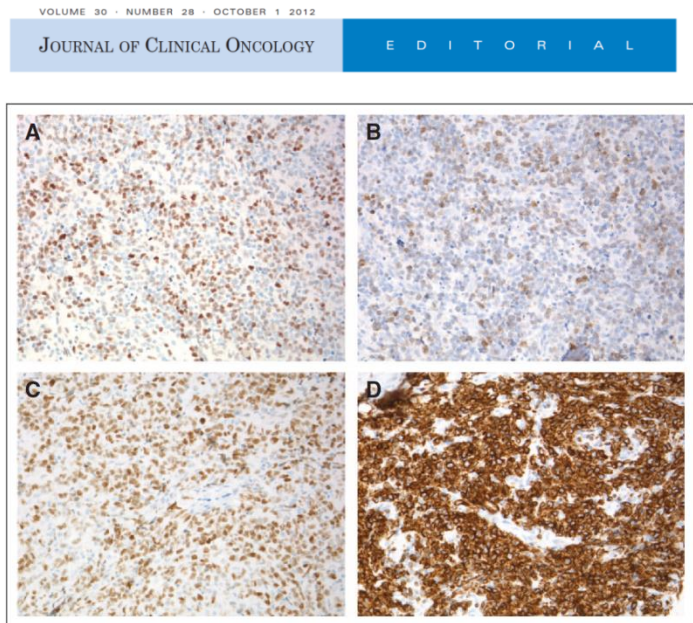
Nanostring Lymph2Cx assay

Scott DW et al, Blood 2014



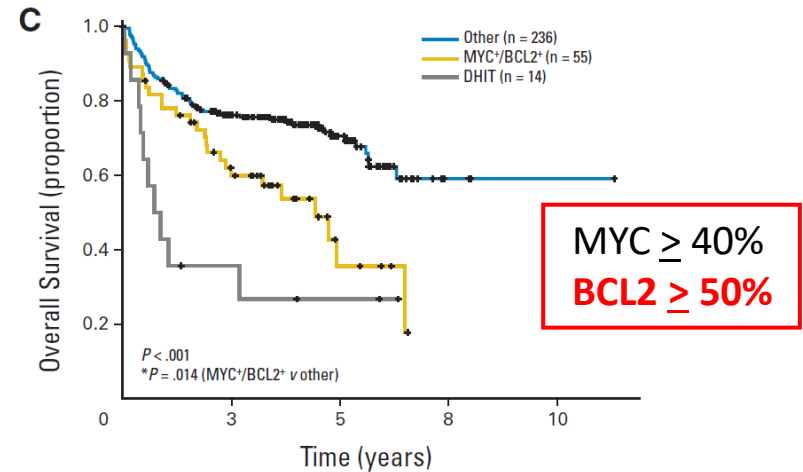
Statut double expresseur (DE)

Immunohistochemical Double-Hit Score Is a Strong Predictor of Outcome in Patients With Diffuse Large B-Cell Lymphoma Treated With Rituximab Plus Cyclophosphamide, Doxorubicin, Vincristine, and Prednisone



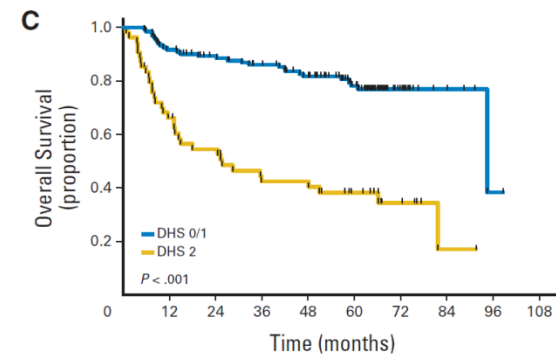
Pfreundschuh M et al, JCO 2012

21% BCL2+/MYC+ (IHC) vs 5% DHL (FISH)



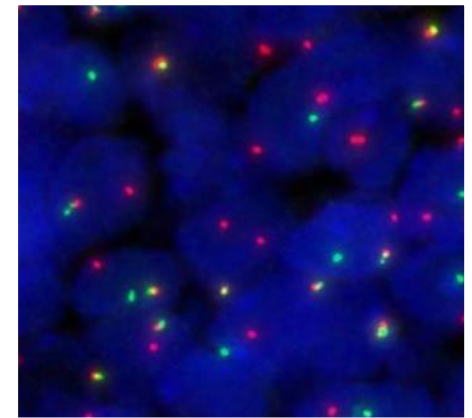
Johnson NA et al, JCO 2012

29% DHS 2 (IHC) vs 6% DHL (FISH)



Green TM et al, JCO 2012

Cytogénétique des LDGCB



- DLBCL, NOS
- PMBL
- Plasmablastic LBCL
- ALK+ LBCL
- Burkitt lymphoma
- HGBL

*BCL2, BCL6, MYC**

*CIITA**

MYC

ALK

MYC

*BCL2, BCL6, MYC**

** Impact Prognostique*

Lymphome B inclassable, intermédiaire entre DLBCL et Lymphome de Burkitt (BCLu) (2008)

2016

**High grade B-cell lymphoma
« double/triple hit »
with *MYC* and *BCL2* (or *BCL6*) R*
(HGBL-DH/TH)**

**High grade B-cell
lymphoma NOS*
(HGBL-NOS)**

Tous les lymphomes B à grandes cellules double-hit

La morphologie doit être précisée:

- **DLBCL**
- intermédiaire DLBCL/Burkitt (BCLu)
- blastoïde

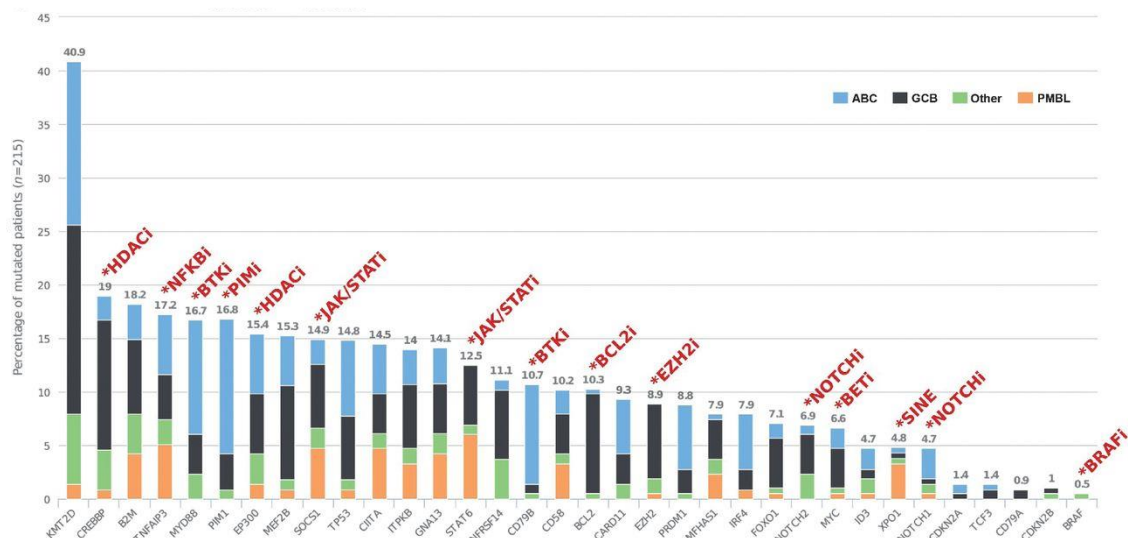
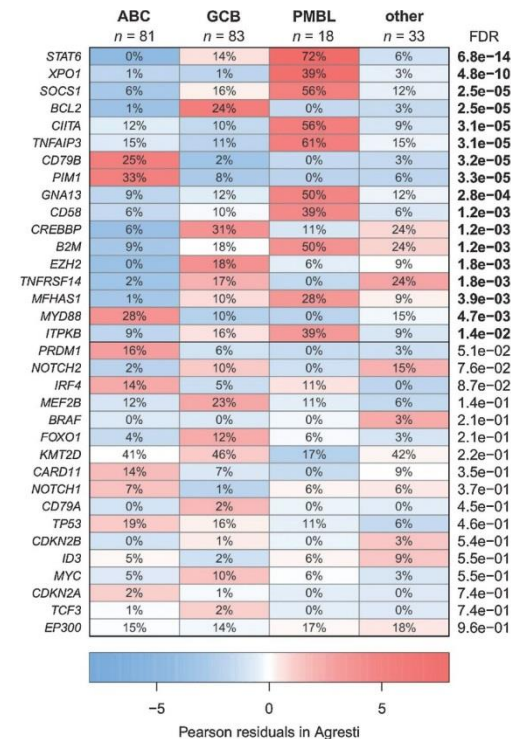
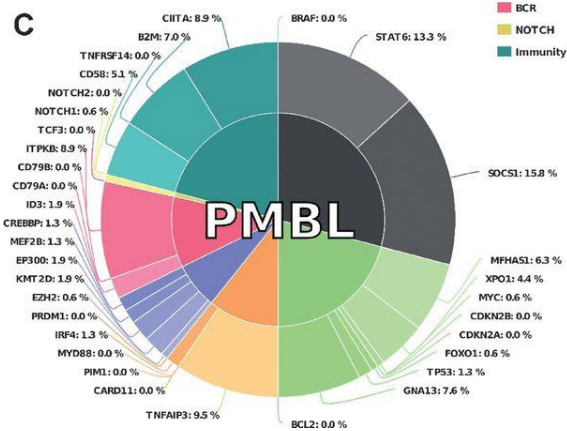
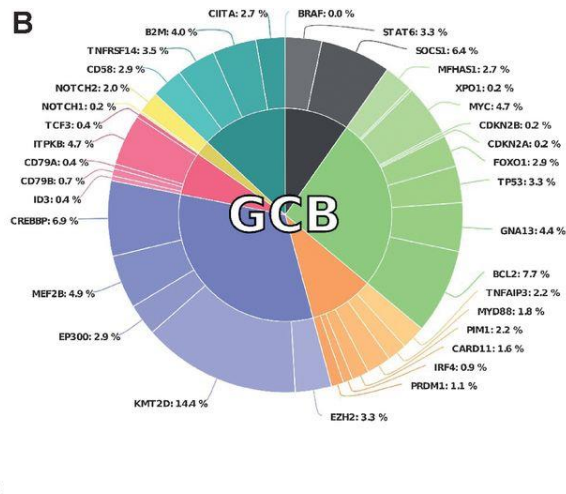
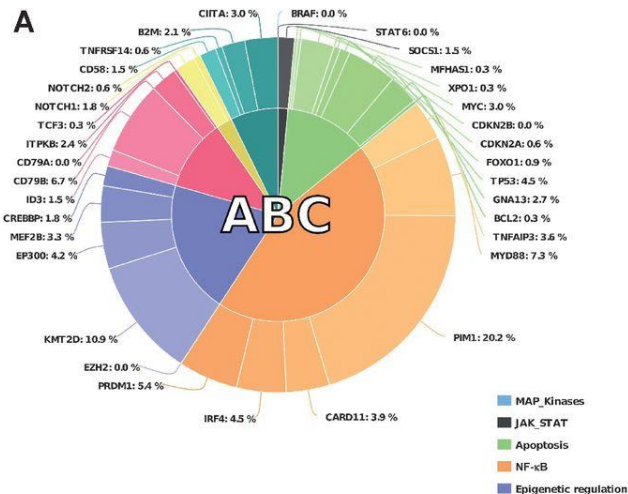
(les lymphomes folliculaires et lymphoblastiques double-hit sont exclus)

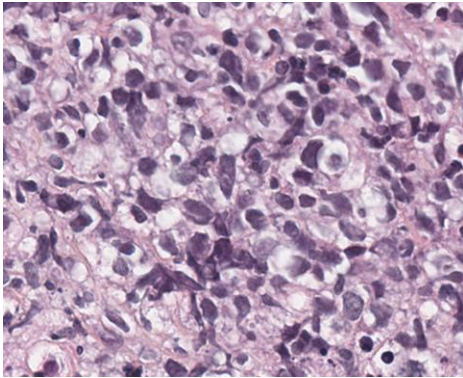
Tous les cas « non-double hit »

de morphologie

- intermédiaire DLBCL/Burkitt (BCLu)
- blastoïde

NGS des LDGCB





Prise en charge diagnostique d'un DLBCL NOS en 2019

• Histopathologie

- *architecture*
diffuse/nodulaire
- *Cytologie*
cbl, ibl, plasmoblastes
- *microenvironnement*:
lymphocytes, éosino,
histiocytes
réseau de FDC

• Panel IHC de base

CD20 CD5

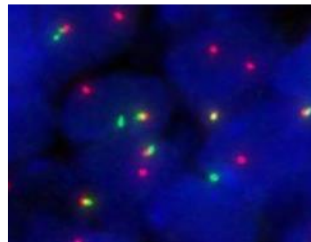
Hans: CD10 BCL6 MUM1

DE: BCL2 MYC

Mib1/Ki67

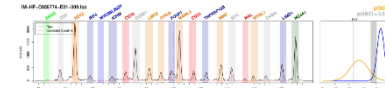
• FISH

- BCL2
- BCL6
- MYC



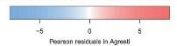
Selon contexte (protocole)

• RT-MLPA



• NGS

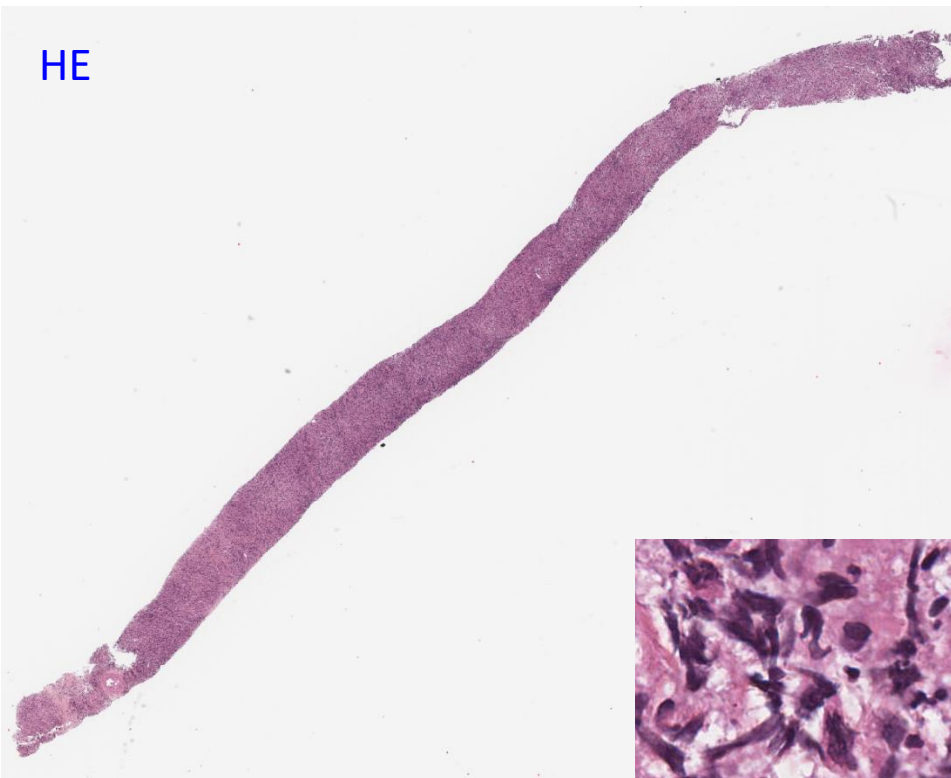
	ABC	GCB	PMBL	other	FDR
BTST1	0%	14%	1%	1%	6.8e-14
SPK1	1%	1%	1%	1%	4.8e-16
BCL11	8%	1%	1%	1%	2.6e-05
BCL2	1%	1%	1%	1%	2.6e-05
CD78	1%	1%	1%	1%	3.1e-05
TROVAP	1%	1%	1%	1%	3.1e-05
CD100	1%	1%	1%	1%	3.2e-05
FABP1	1%	1%	1%	1%	3.3e-05
CD43	1%	1%	1%	1%	2.8e-04
FABP5	1%	1%	1%	1%	3.3e-04
CD183	1%	1%	1%	1%	1.2e-03
CD38	1%	1%	1%	1%	1.2e-03
CD103	1%	1%	1%	1%	1.2e-03
CD58	1%	1%	1%	1%	1.2e-03
CD137	1%	1%	1%	1%	1.2e-03
CD27	1%	1%	1%	1%	1.2e-03
CD28	1%	1%	1%	1%	1.2e-03
CD40	1%	1%	1%	1%	1.2e-03
CD80	1%	1%	1%	1%	1.2e-03
CD86	1%	1%	1%	1%	1.2e-03
TIMEP3L4	1%	1%	1%	1%	1.2e-03
HAVCR1	1%	1%	1%	1%	3.8e-03
CD279	1%	1%	1%	1%	4.7e-03
HAVCR2	1%	1%	1%	1%	1.1e-02
CD276	1%	1%	1%	1%	2.5e-02
CD277	1%	1%	1%	1%	3.5e-02
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CD397	1%	1%	1%	1%	3.5e-02
CD398	1%	1%	1%	1%	3.5e-02
CD399	1%	1%	1%	1%	3.5e-02
CD400	1%	1%	1%	1%	3.5e-02



Pièges et limites

3 exemples

HE



CAS 1

M, 36 ans

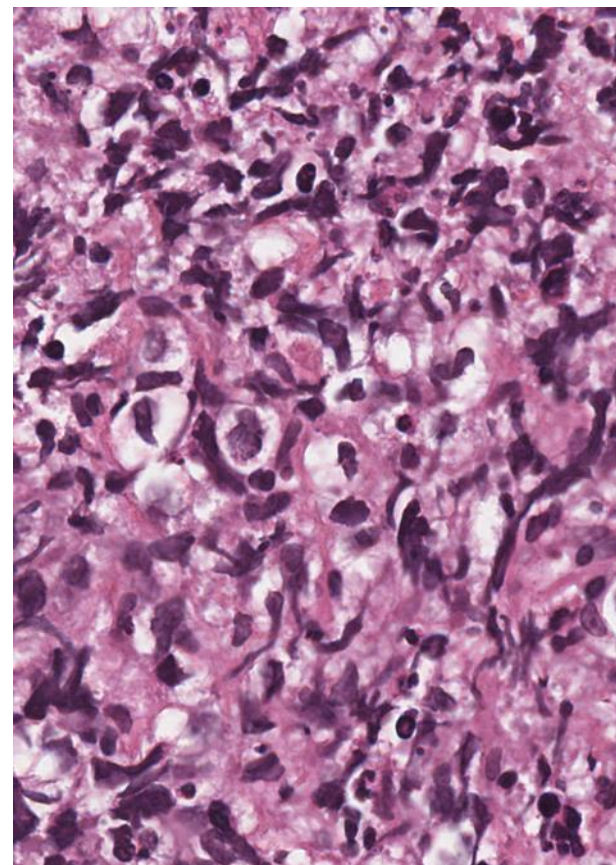
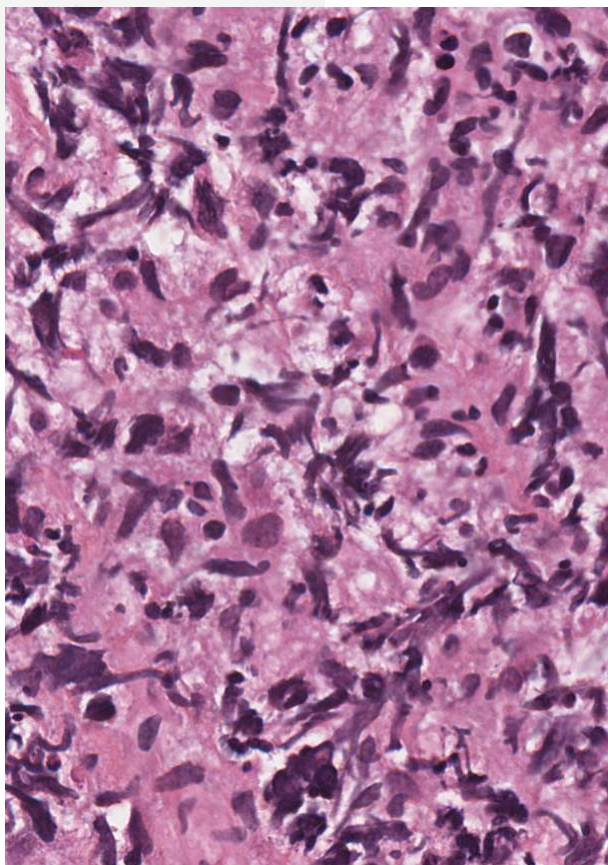
Ictère

Tumeur duodénale comprimant les voies
biliaires

PET: atteinte pulmonaire, médiastinale

LDH 344, Stade IV

Biopsie à l'aiguille
de la masse
médiastinale



Hypothèses diagnostiques?

- Carcinome?
- Tumeur neuroendocrine?
- DLBCL-NOS?
- PMBL?
- Lymphome lymphoblastique?
- Thymome?



Premier panel: CD20, CD5, AE1/AE3, CD56



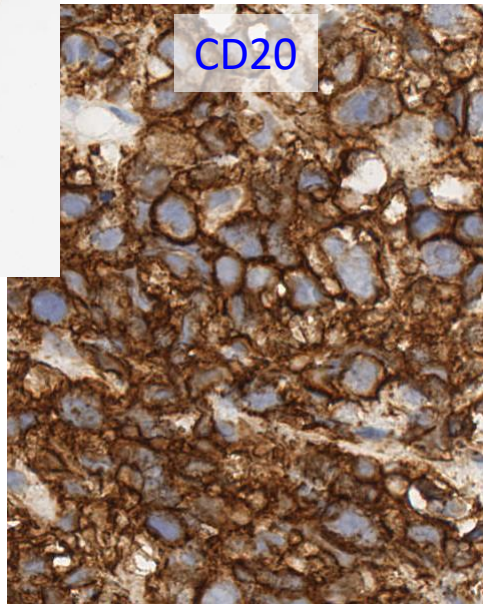
CD20+, CD5-, AE1/AE3-, CD56-

Panel IHC DLBCL

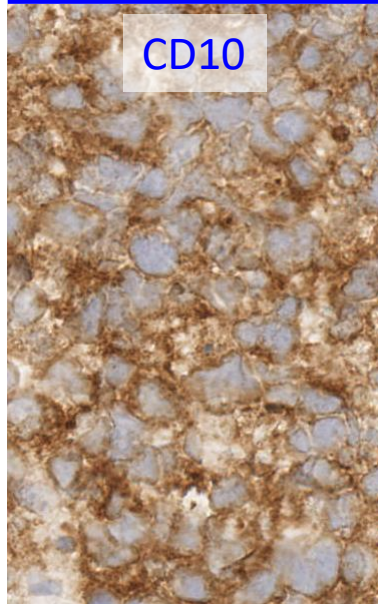
Hans : GC



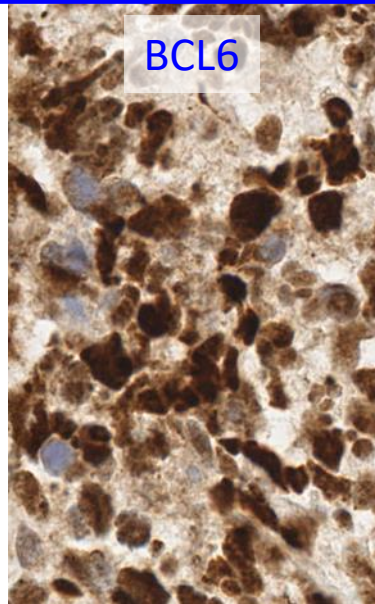
CD20



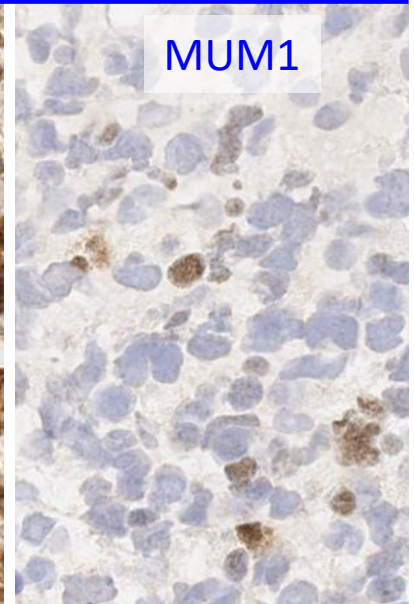
CD20



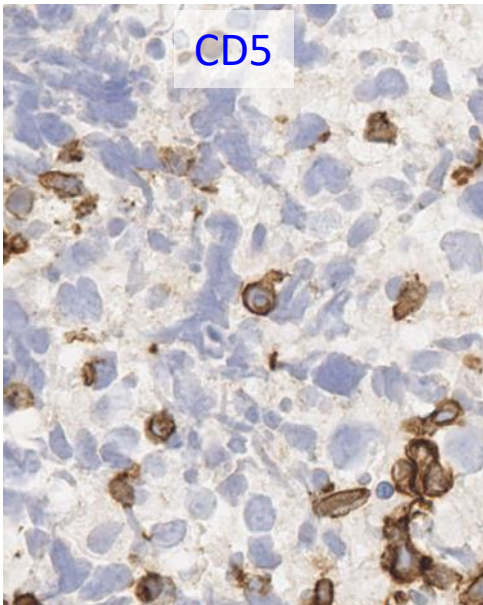
CD10



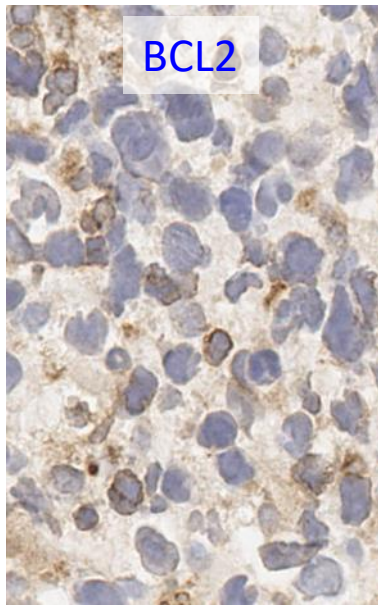
BCL6



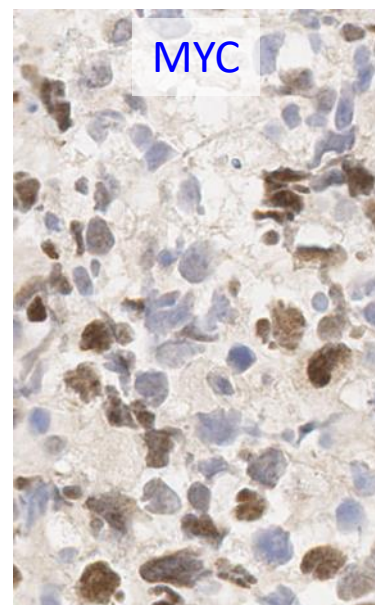
MUM1



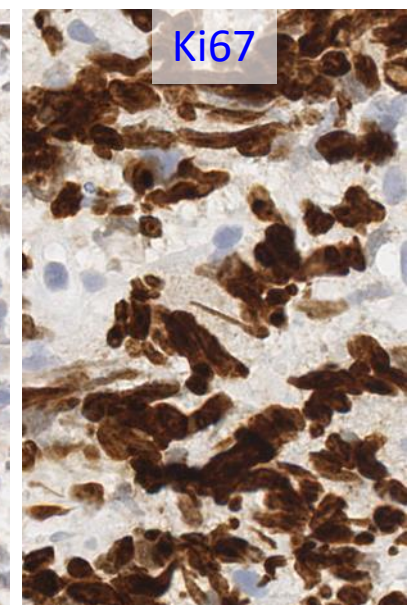
CD5



BCL2



MYC

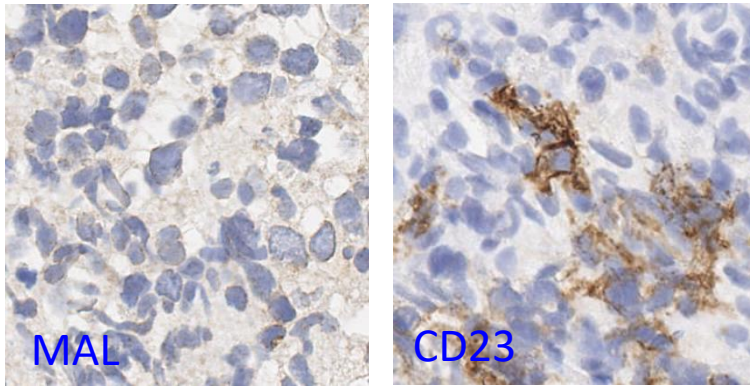


Ki67

Analyses complémentaires

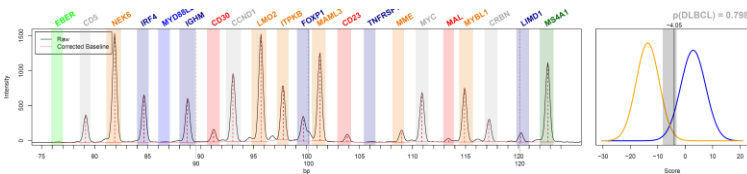
CR final

- IHC: MAL-, CD23+het, CD30-, PDL1-



- FISH: BCL2- BCL6- MYC-, CIITA+

- RT-MLPA: inclassable entre DLBCL et PMBL



- NGS: mutations de TNFAIP3, SOCS1, B2M, STAT6 et CREBBP, CXCR4

Matériel biologique	médiastin	Diagnostic	FFPE
Date réception :	31/01/0219	ADN	83
% cellules tumorales :	80%	V (µL)	50
		ARN	101
		V (µL)	50

Histologie	DLBCL	commentaire :
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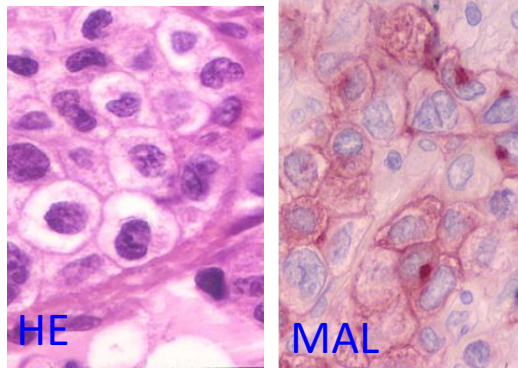
PHENOTYPE	GENOTYPE
HANS <input type="text" value="GC"/> CD10+ BCL6+ MUM1- RT-MLPA <input type="text" value="Non classé DLBCL/PMBL"/> p= 0,2 <input type="checkbox"/> MYD88 L265P <input type="checkbox"/> EBV IHC BCL2 <input type="text" value="0%"/> positif si ≥50% IHC MYC <input type="text" value="20%"/> positif si ≥40% Double expresseur MYC/BCL2 NON commentaire :	S5 - life technologies <input type="checkbox"/> MYD88 L265P <input type="checkbox"/> MYD88 S219C <input type="checkbox"/> MYD88 S243N <input type="checkbox"/> EZH2 Y646 <input type="checkbox"/> CD79B Y196 <input type="checkbox"/> BRAF V600E B2M, CREBBP, CXCR4, SOCS1, STAT6, TCF3, TNFAIP3 CLONALITE : <u>Non réalisé</u> commentaire :

FISH			
BCL2	BCL6	MYC	MYC PARTENAIRE
non réarrangé	non réarrangé	non réarrangé	non réalisé
commentaire : CIITA réarrangé			

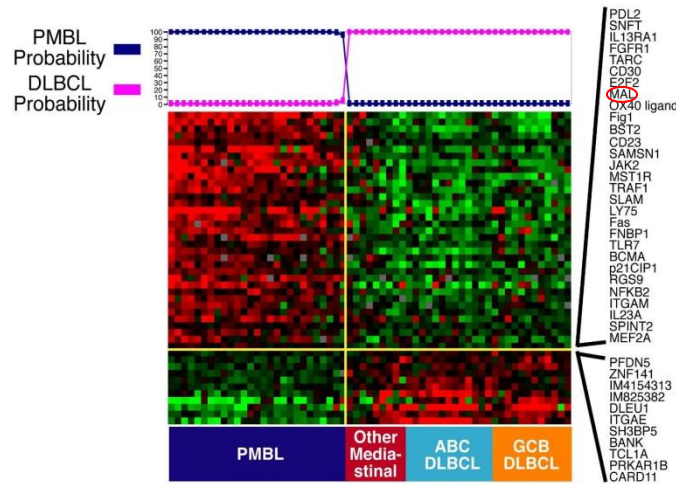
CONCLUSION
DLBCL DE TYPE GC SELON HANS, INCLASSE EN RT-MLPA , AVEC REARRANGEMENT DE CIITA, DE CLASSIFICATION DIFFICILE ENTRE DLBCL NOS ET PMBL, D'AUTANT QUE LE PROFIL MUTATIONNEL AVEC MUTATIONS DE B2M, SOCS1, TNFAIP3, STAT6 SUGGERE UN PMBL.

PMBL

Sujet jeune
 Masse médiastinale
 Cellules claire, fibrose
 MAL+ CD23+ CD30+ PDL1+



GEP



Voies de signalisation

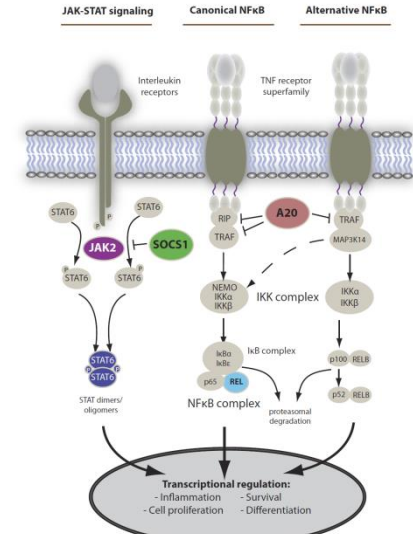
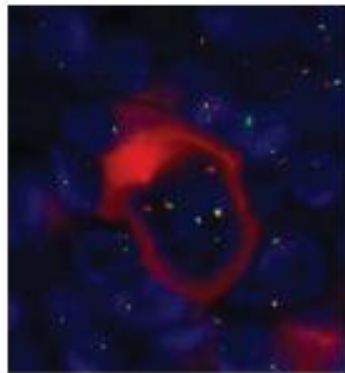


Figure 2. Main deregulated signaling pathways in PMBL. The main activation cascades of JAK-STAT and NF- κ B signaling. Alternative pathway activation exists. Known gene alterations leading to constitutive pathway activity in PMBL are shown in color.

Table 1. Recurrent gene alterations involved in the pathogenesis of primary mediastinal B-cell lymphoma

Gene	Pathway/function	Frequency of alteration in PMBL, % (primary reference)
Copy number gain		
<i>REL</i>	NF- κ B pathway	75 (45)
<i>PDL1/PDL2</i>	Induction of T-cell exhaustion/apoptosis	63 (10)
<i>JAK2</i>	IL/JAK-STAT pathway/histone modification	63 (10)
<i>JMJD2C</i>	Histone modification	63 (61)
Chromosomal translocation/rearrangement		
<i>CIITA</i>	Transcriptional regulation of HLA class II/antigen presentation	38 (11)
Coding sequence mutation		
<i>SOCS1</i>	IL/JAK-STAT pathway	45 (64)
<i>STAT6</i>	IL/JAK-STAT pathway	36 (68)
<i>TNFAIP3</i>	NF- κ B pathway	36 (4)
<i>MYC</i>	Transcriptional regulation/chromatin remodeling	25 (42)
<i>TP53</i>	p53 pathway	13 (42)
Promoter hypermethylation		
<i>p16/INK</i>	Cell-cycle progression, p53 pathway	9 (42)



FISH CIITA

CAS 2

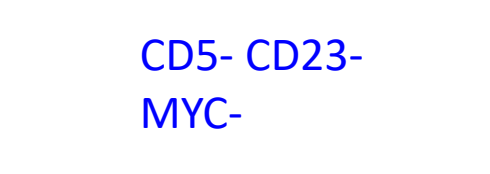
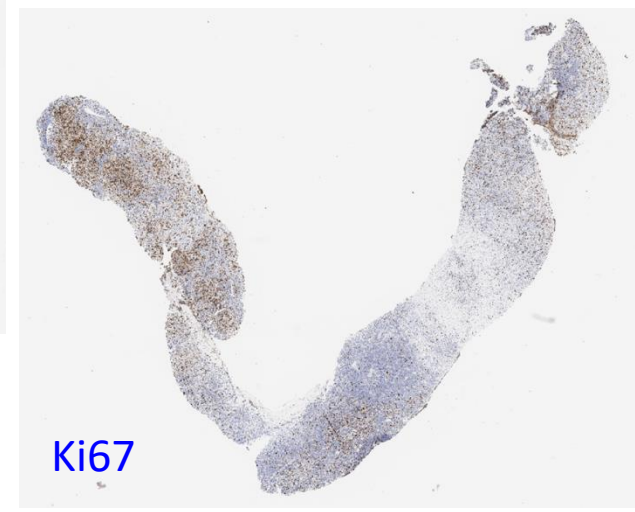
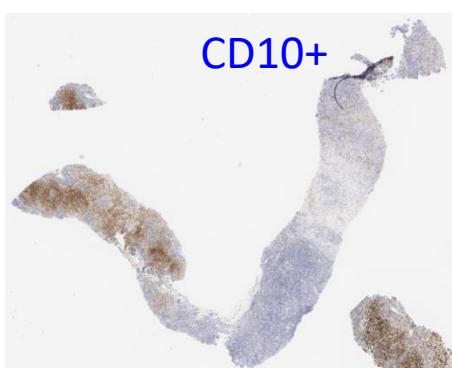
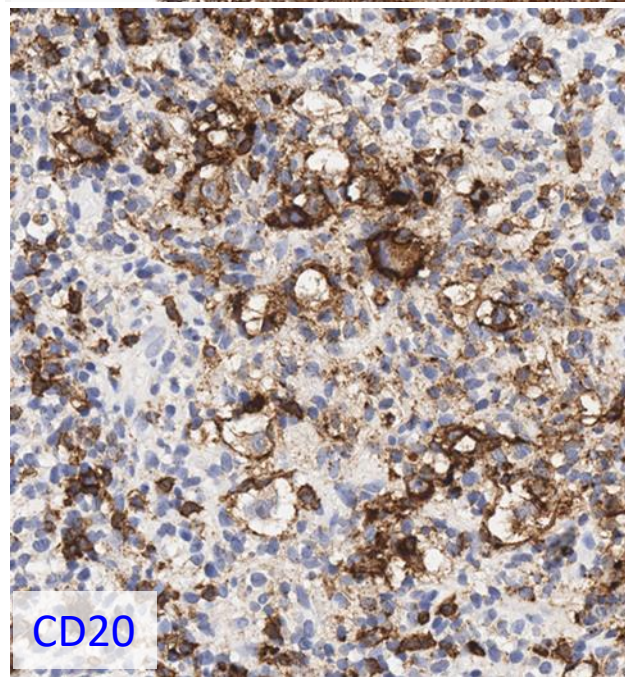
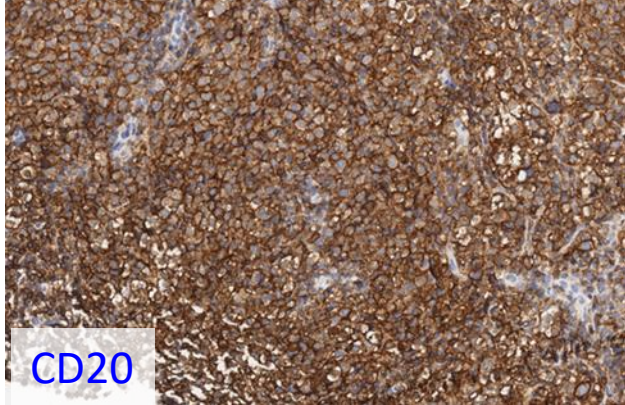
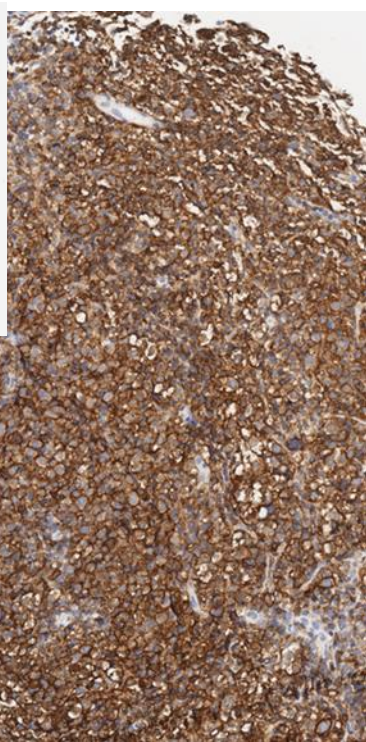
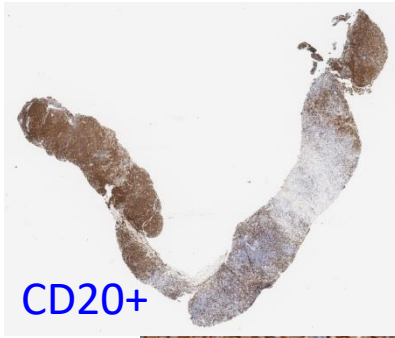
- F, 55y, atcd K sein
- Ganglion inguinal évoluant depuis 2016, modification récente

HE

DLBCL?

LF?

Hodgkin?



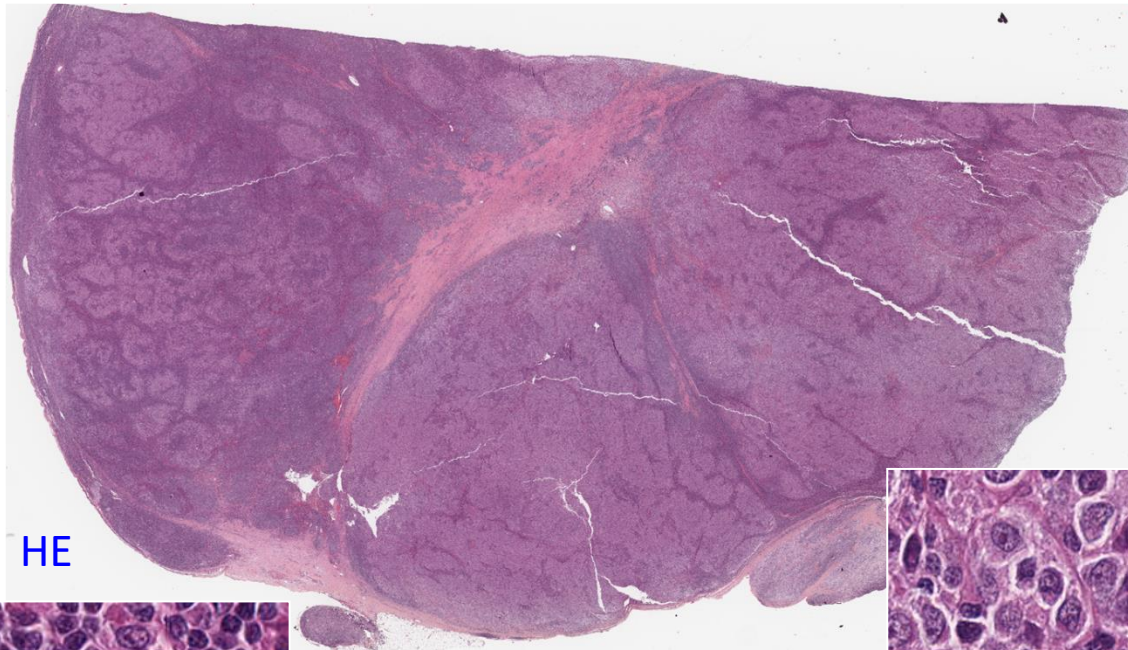
Diagnostique?

- Lymphome B de sous classification difficile dans les limites de cette petite biopsie:
 - Présence d'un contingent de cellules B centrofolliculaires (CD20+ CD10+ BCL6+ BCL2-, CD23-)
 - Contingent de cellules de grande taille « sternbergoïdes » CD20+ CD30+ pouvant faire discuter une progression cytologique?

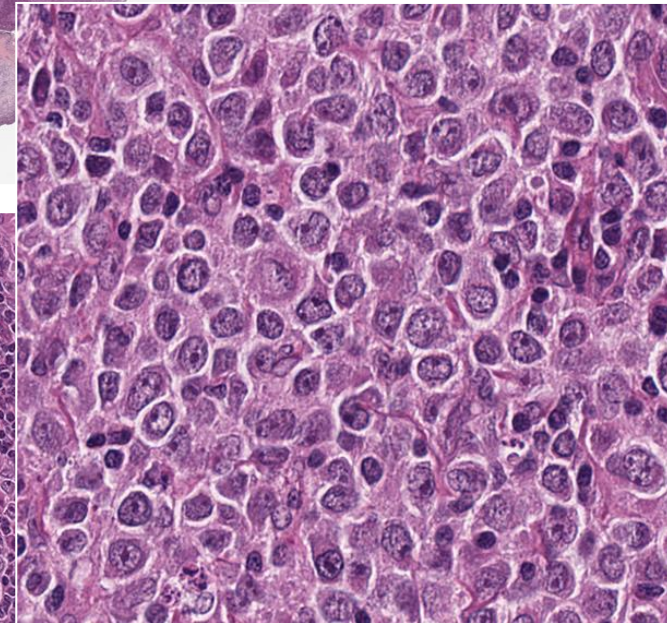
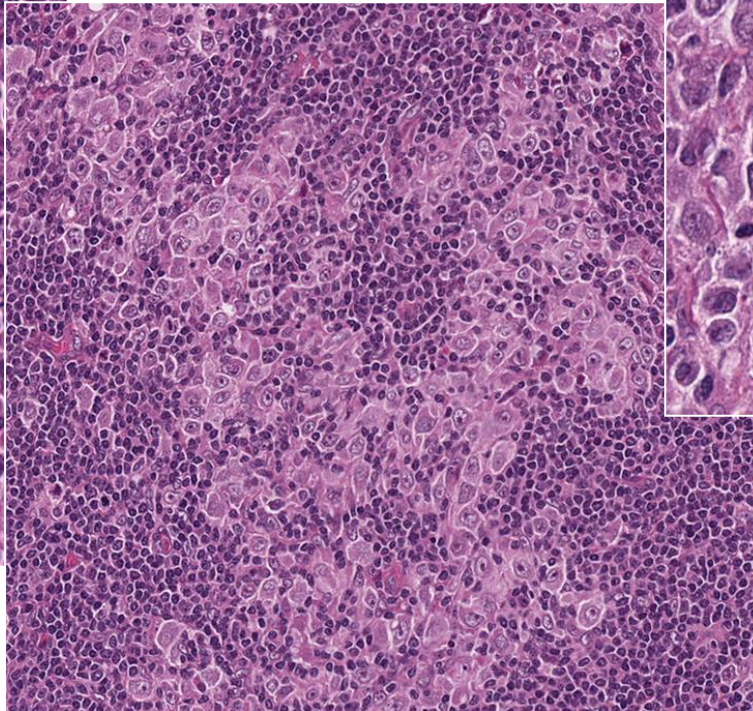
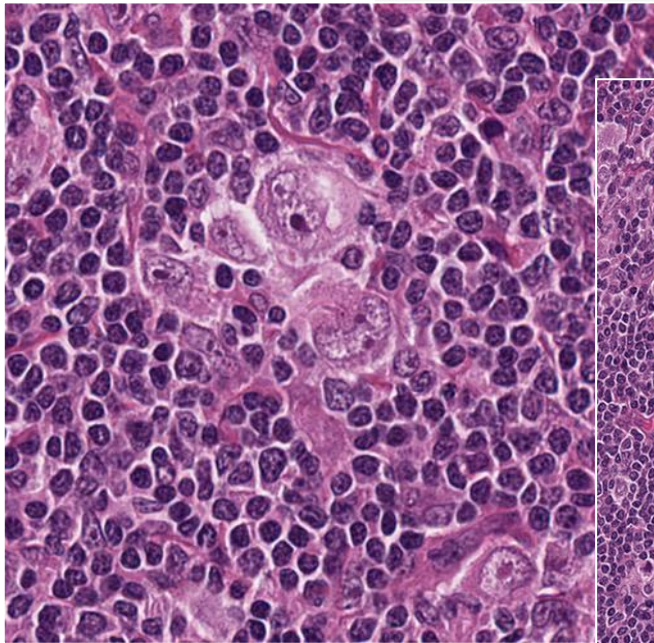
→ une biopsie exérèse chirurgicale est nécessaire

CAS 2

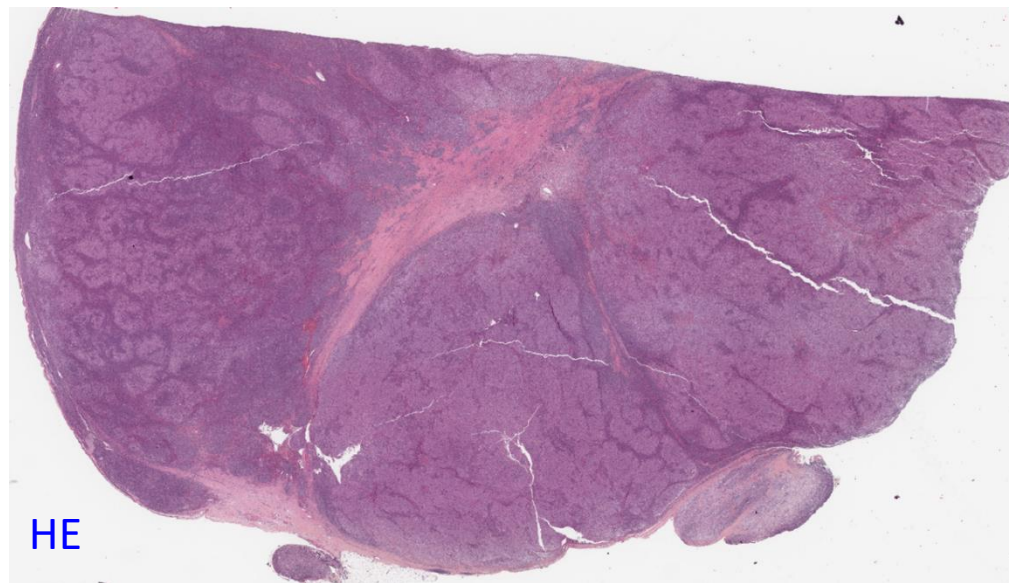
biopsie exérèse
chirurgicale
Ganglion
inguinal



HE



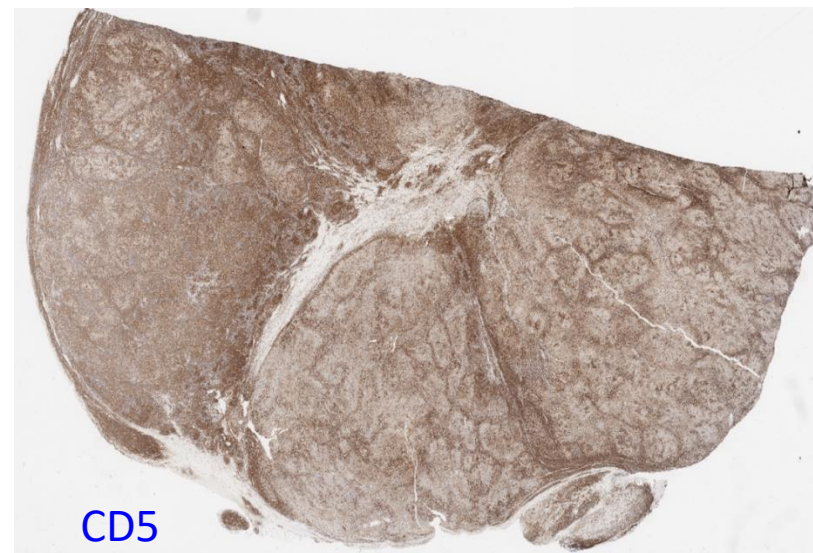
CAS 2



HE



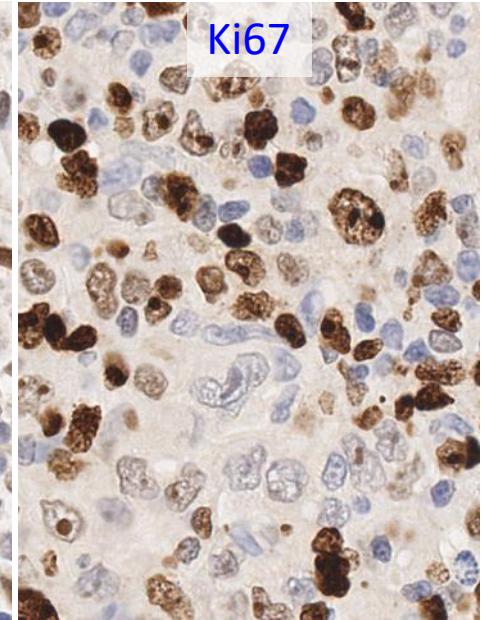
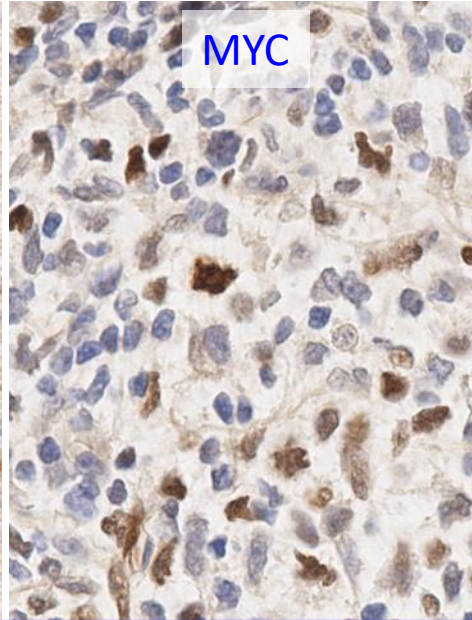
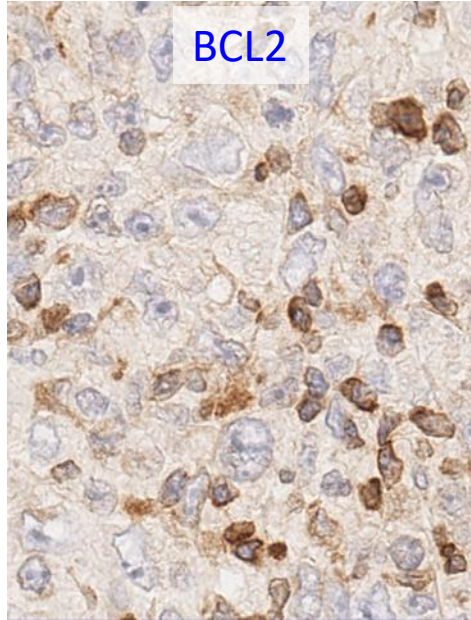
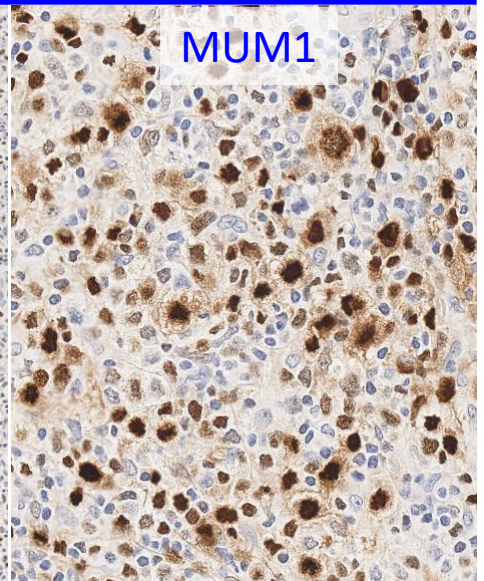
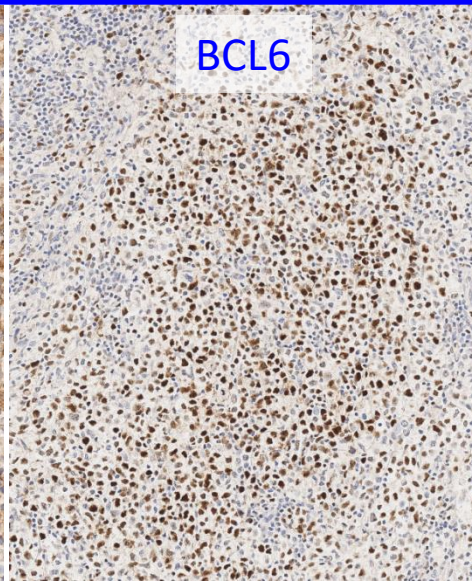
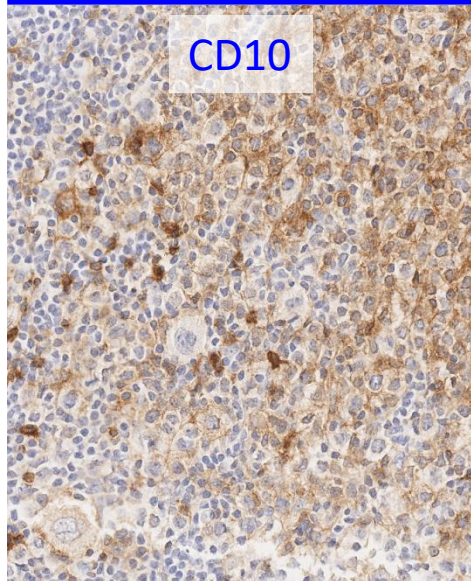
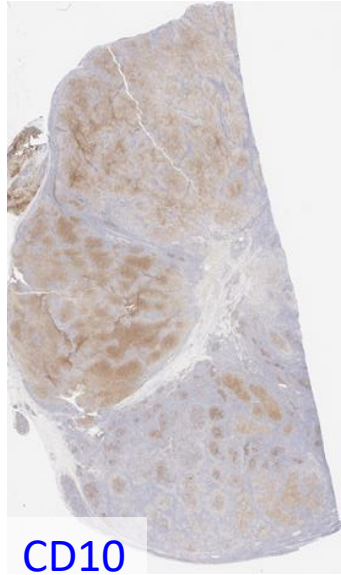
CD20



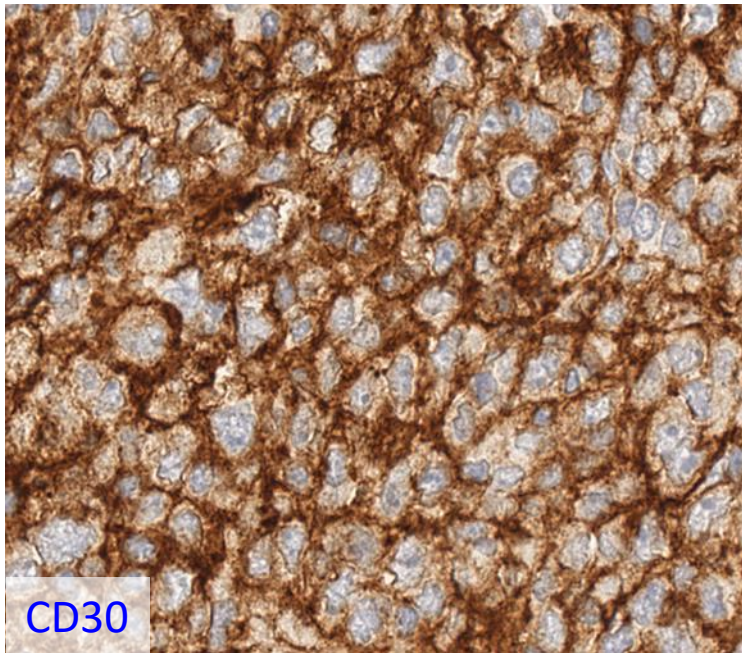
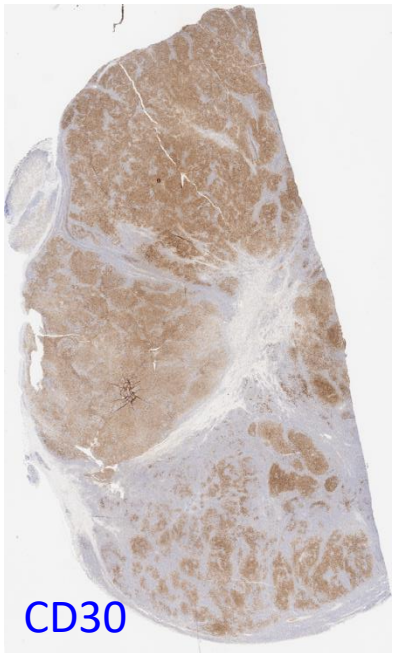
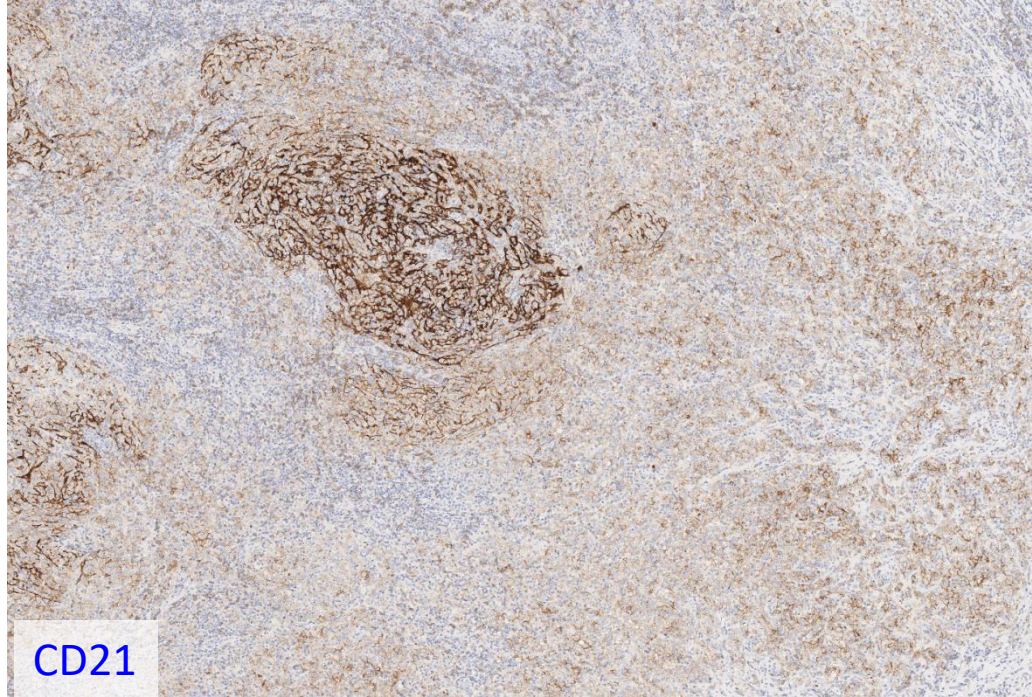
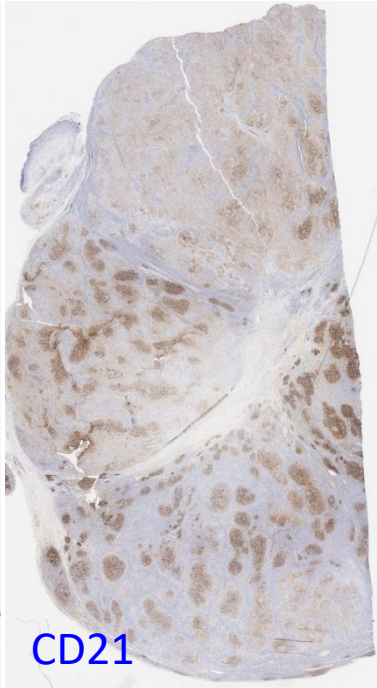
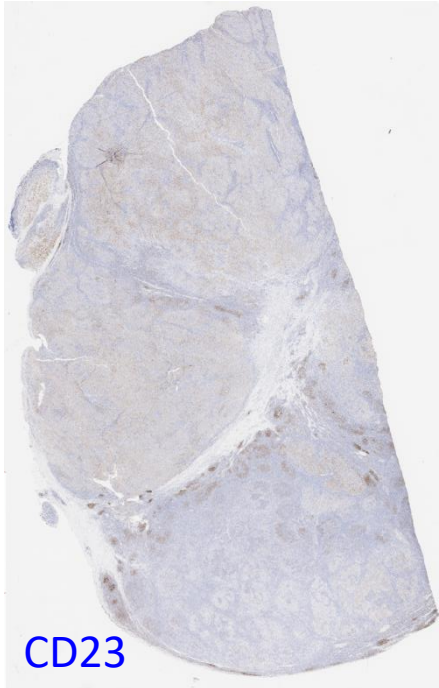
CD5

IHC

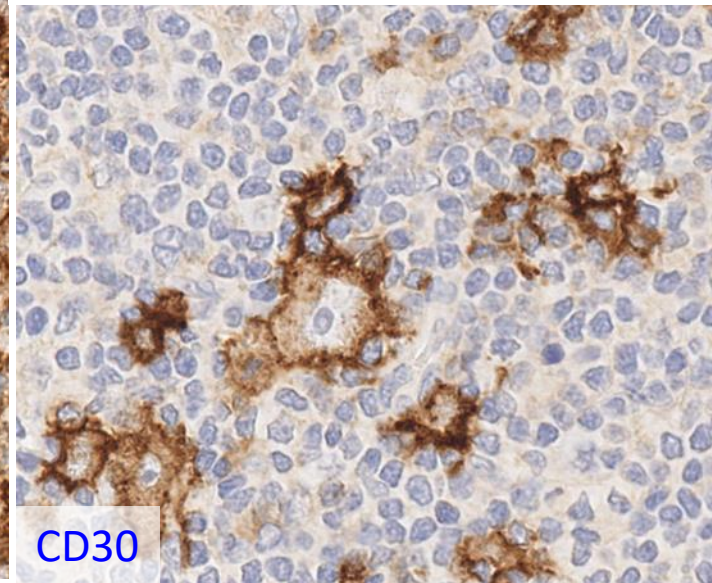
Hans : GC



DE -



Analyses FISH: BCL2- BCL6- MYC-



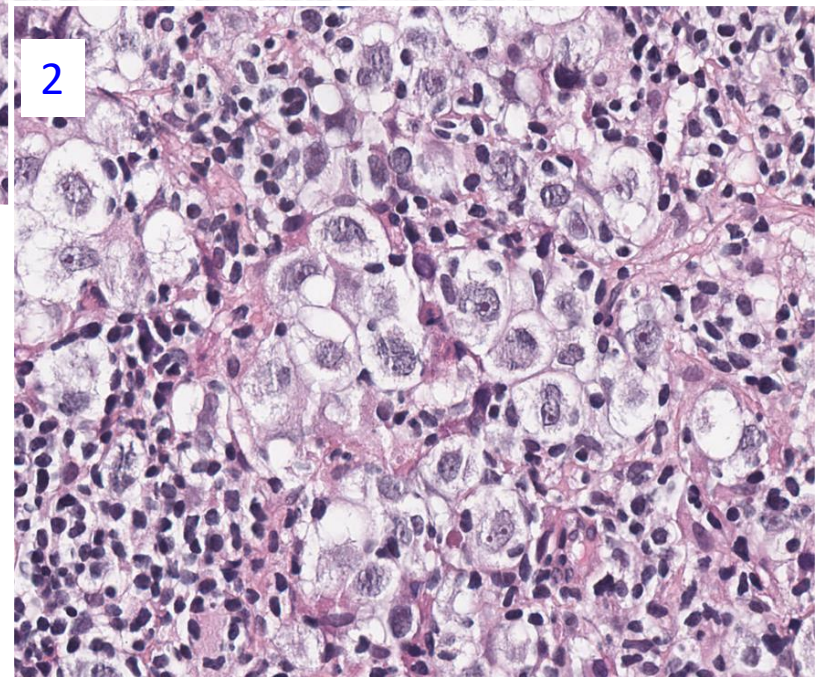
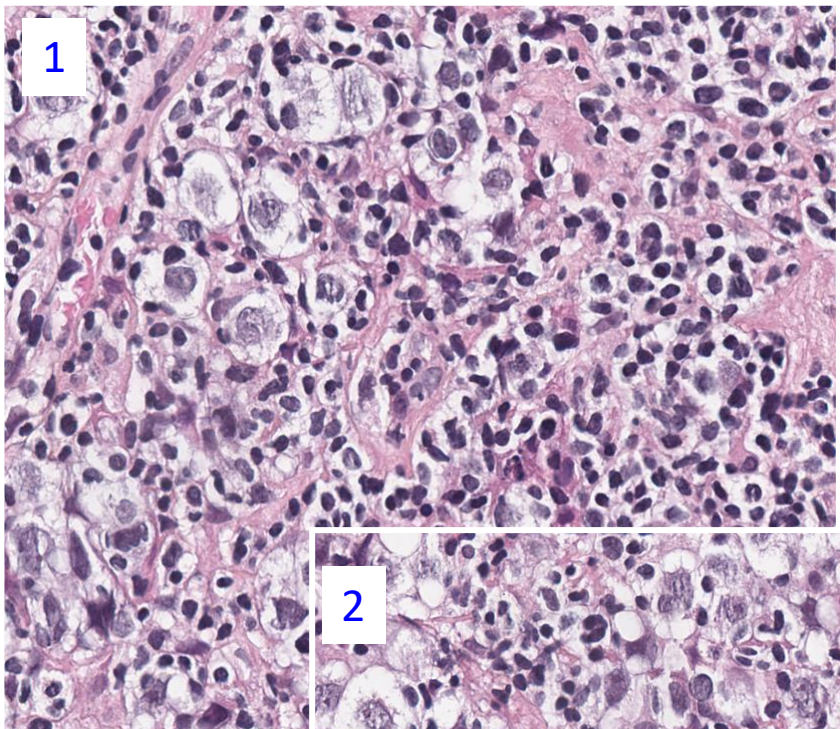
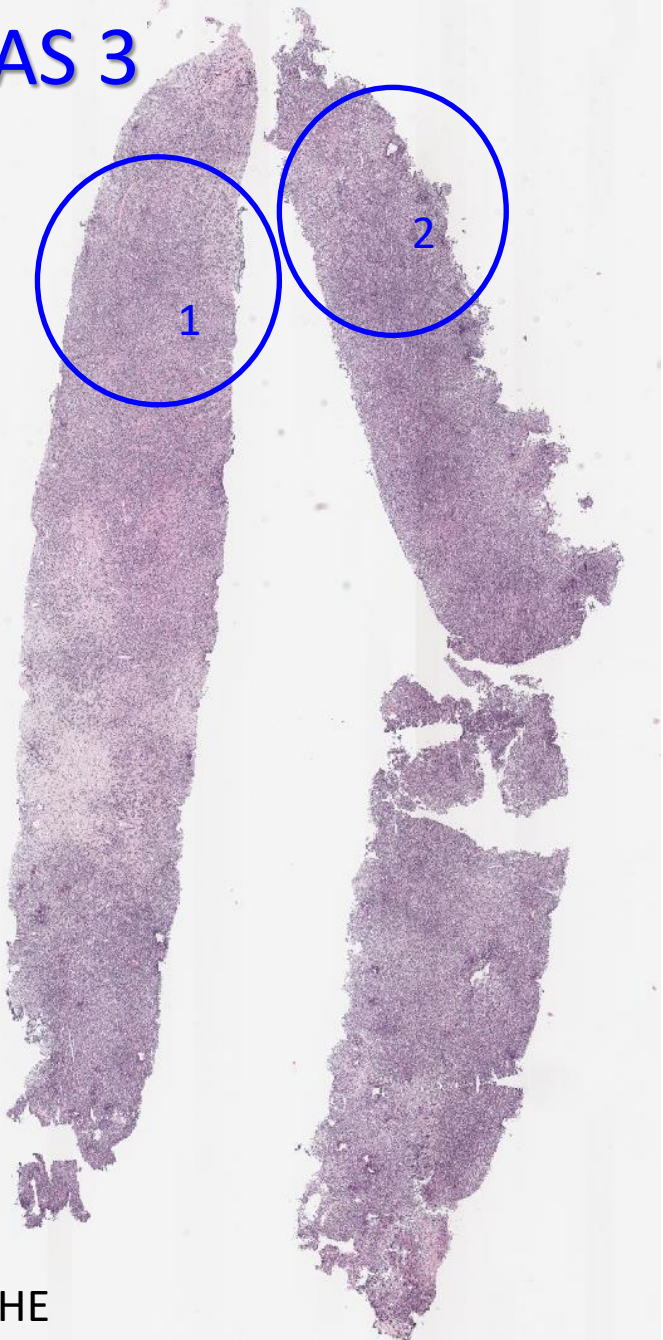
Diagnostic retenu

- Lymphoprolifération B à grandes cellules, d'origine centrofolliculaire (CD10+ BCL6+) , d'architecture nodulaire et plus partiellement diffuse, particulière par l'expression du CD30+.

→ DLBCL-NOS de type GC avec des secteurs de lymphome folliculaire 3B, DE-, avec expression du CD30, sans réarrangement détectable des gènes *BCL2*, *BCL6* et *MYC*.

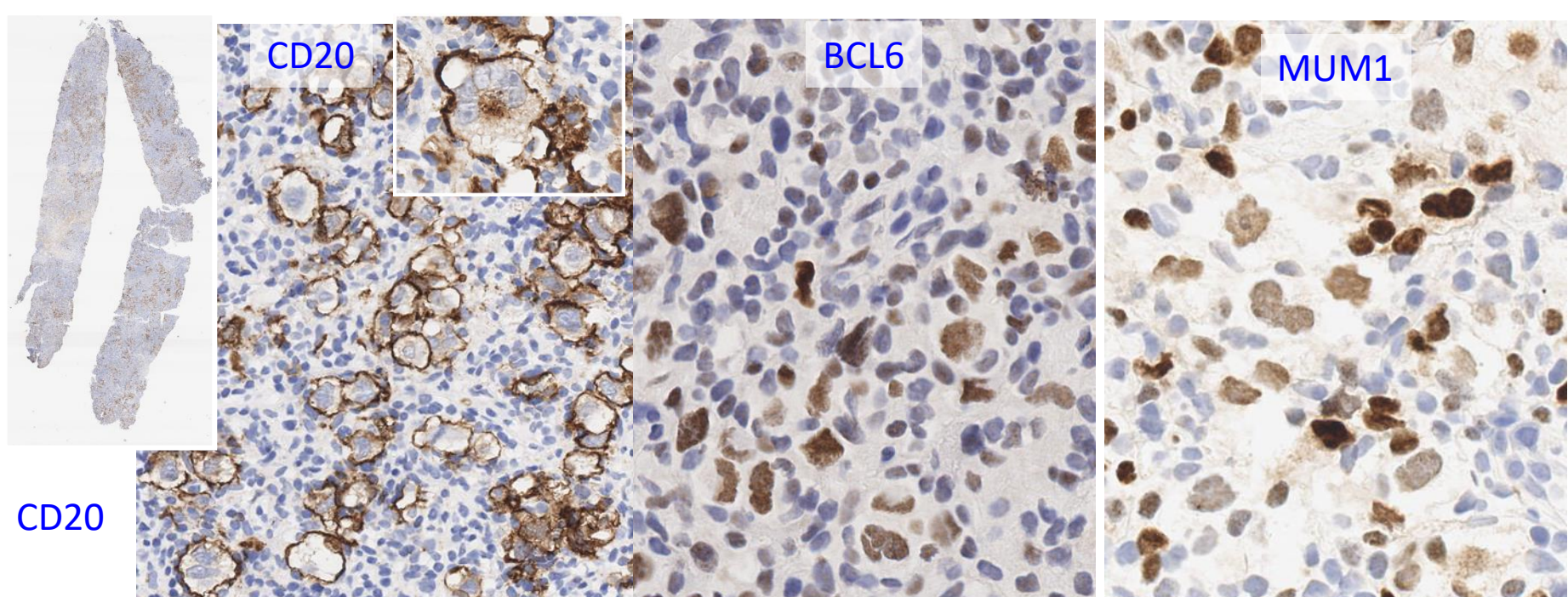
CAS 3

M, 45y, adénopathie axillaire droite , 2 nodules sous hépatiques de 6cm, sans altération de l'état général.

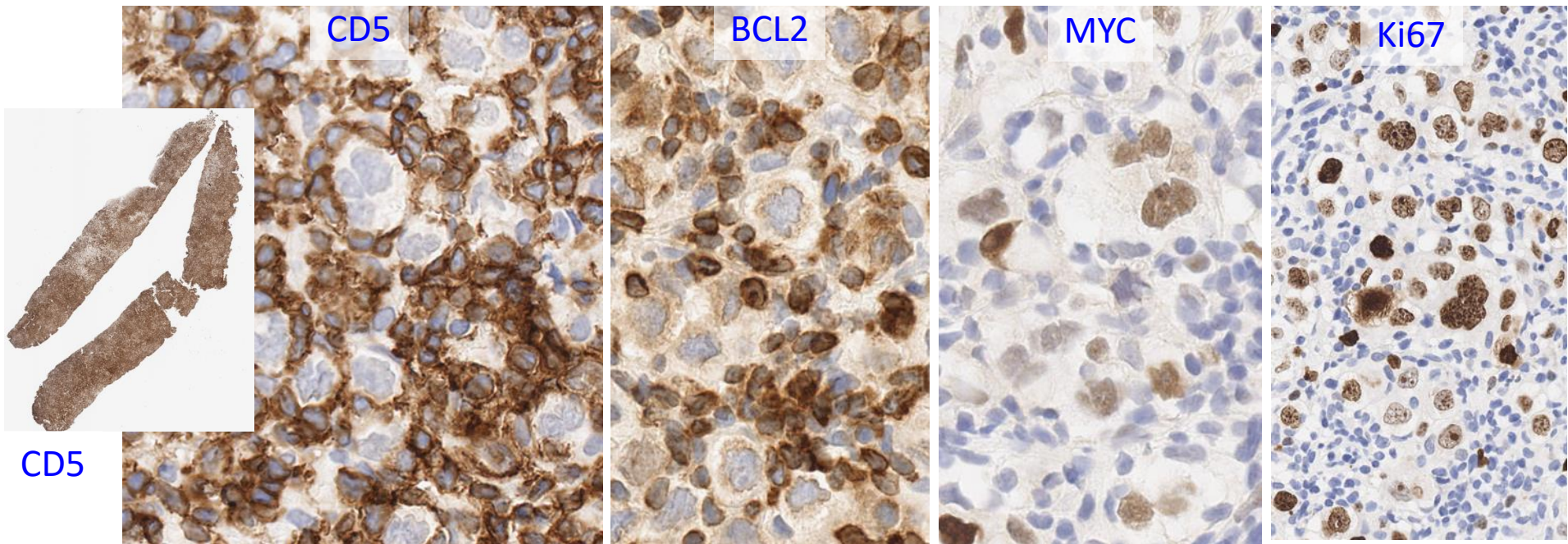


Hodgkin?
TCRBCL?

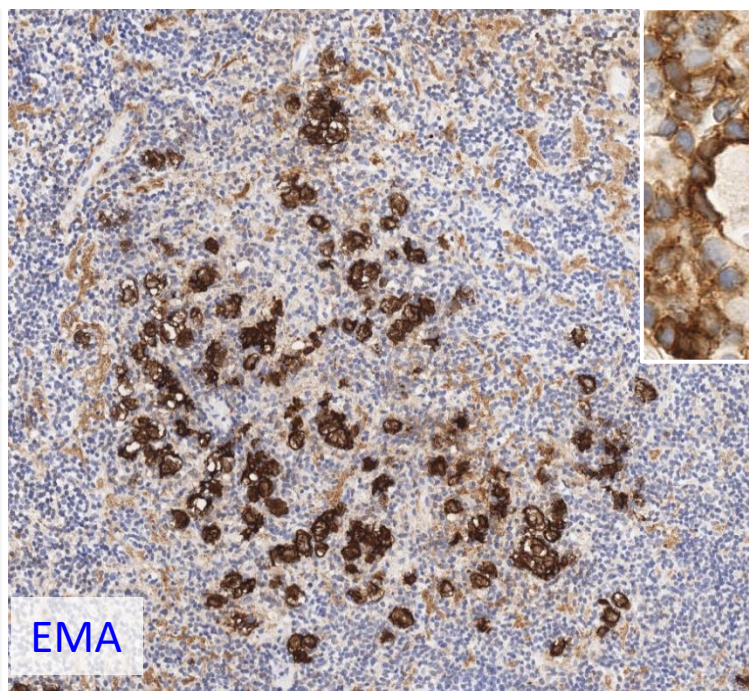
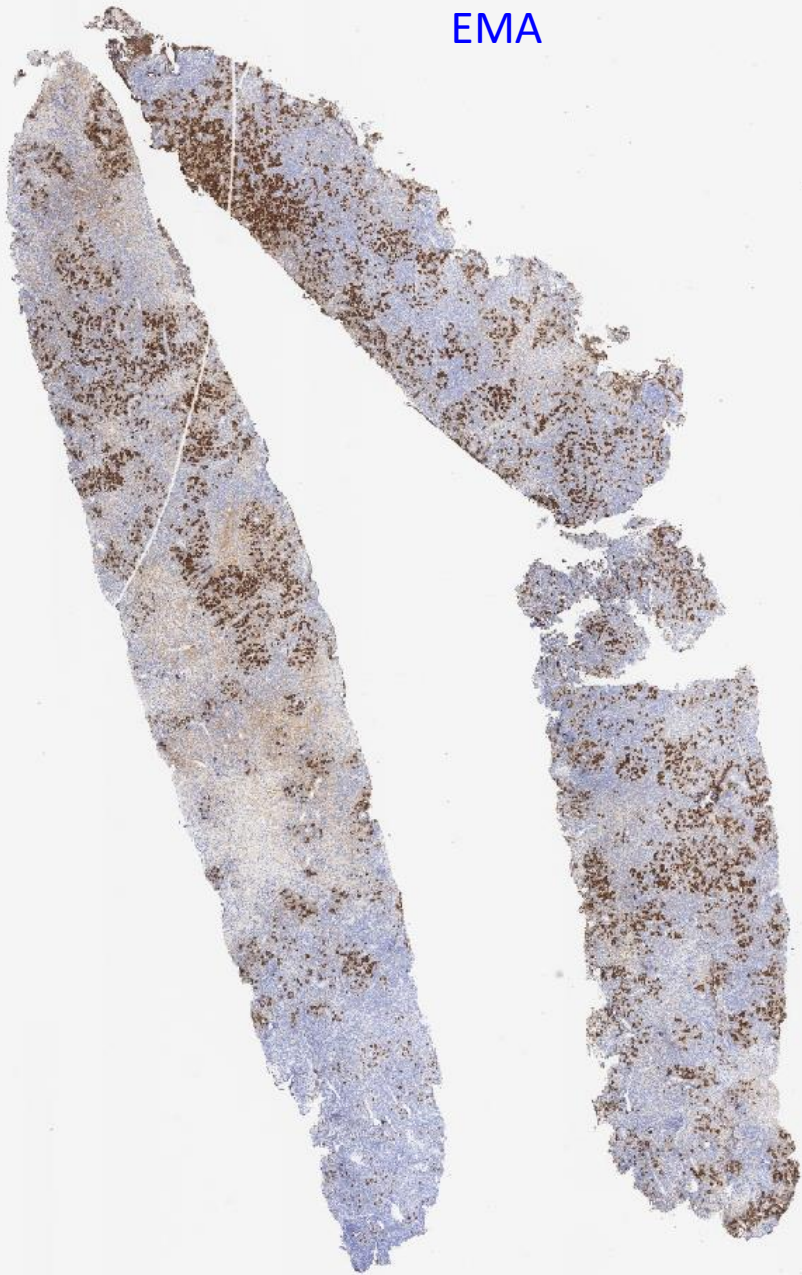
DLBCL?
LF3B?



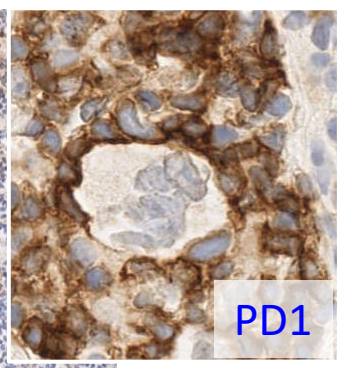
CD20+ CD5- CD10- BCL6+ MUM1+ BCL2 + faible, MYC<40%, CD21- CD23- CD30- CD15- Ki67 élevé, EBERS-



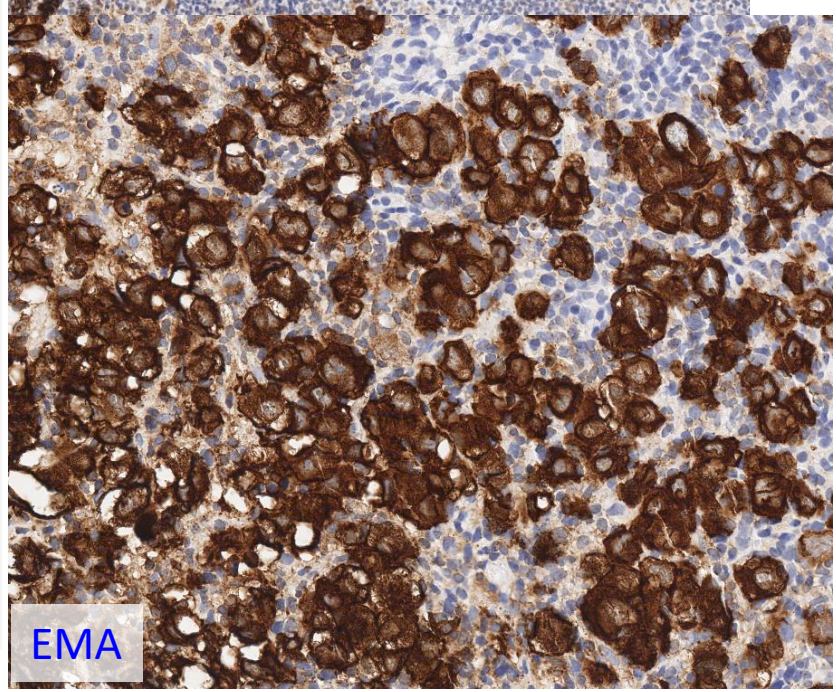
EMA



EMA



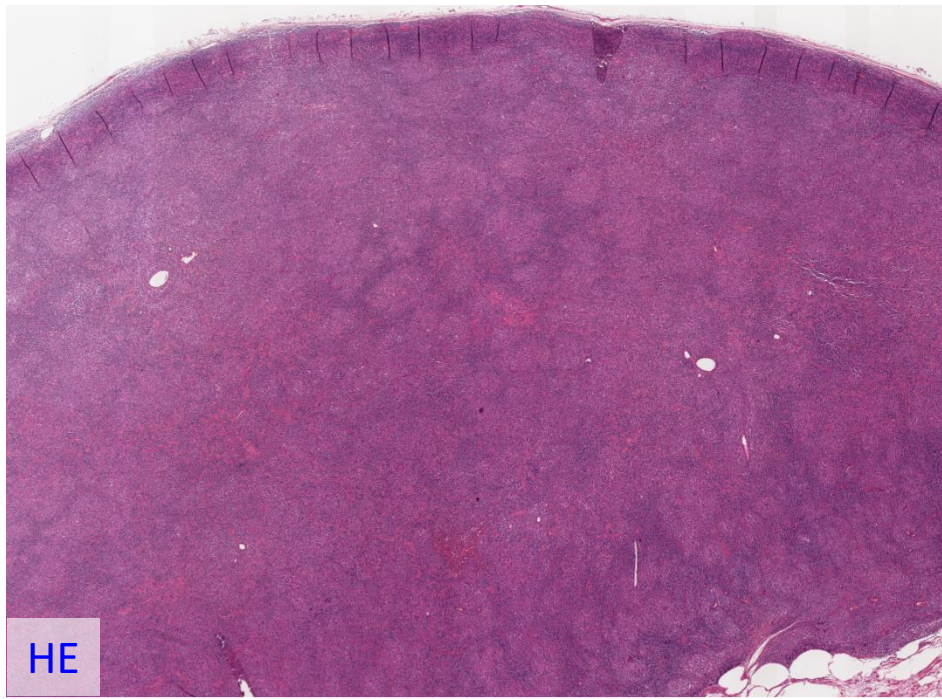
PD1



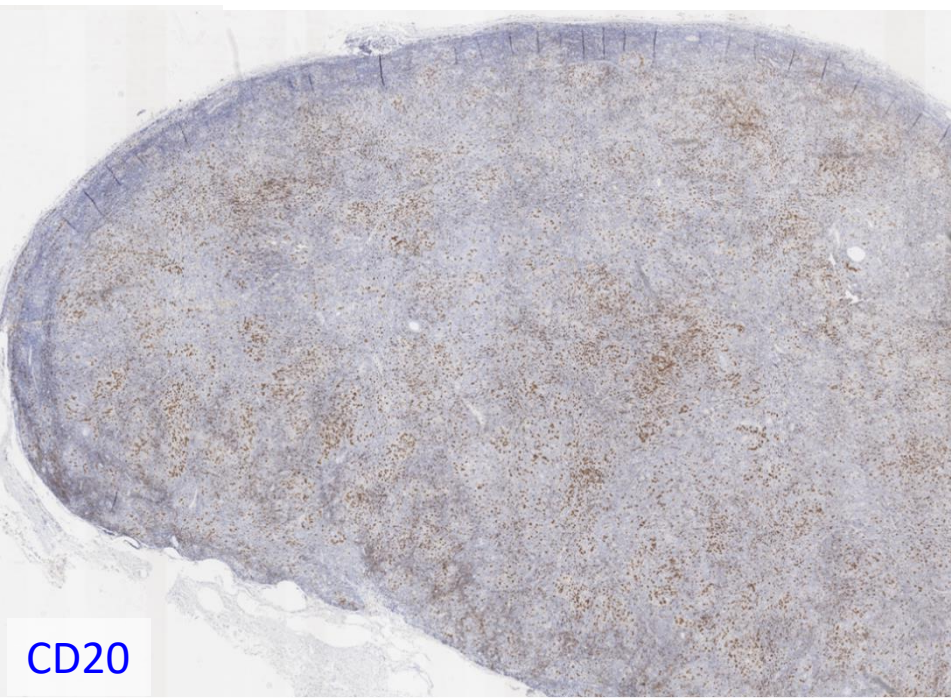
EMA

Diagnostic proposé

- Dans les limites de ce biopsies, ces aspects font discuter:
 - En premier lieu Lymphome de Hodgkin nodulaire à prédominance lymphocytaire (Paragranulome de Poppema)
 - Il est difficile d'écarter formellement une transformation en LDGCB ou un lymphome B à grandes cellules riche en histiocytes et lymphocytes T (TCRBCL).
- une biopsie exérèse chirurgicale de l'adénopathie axillaire est nécessaire

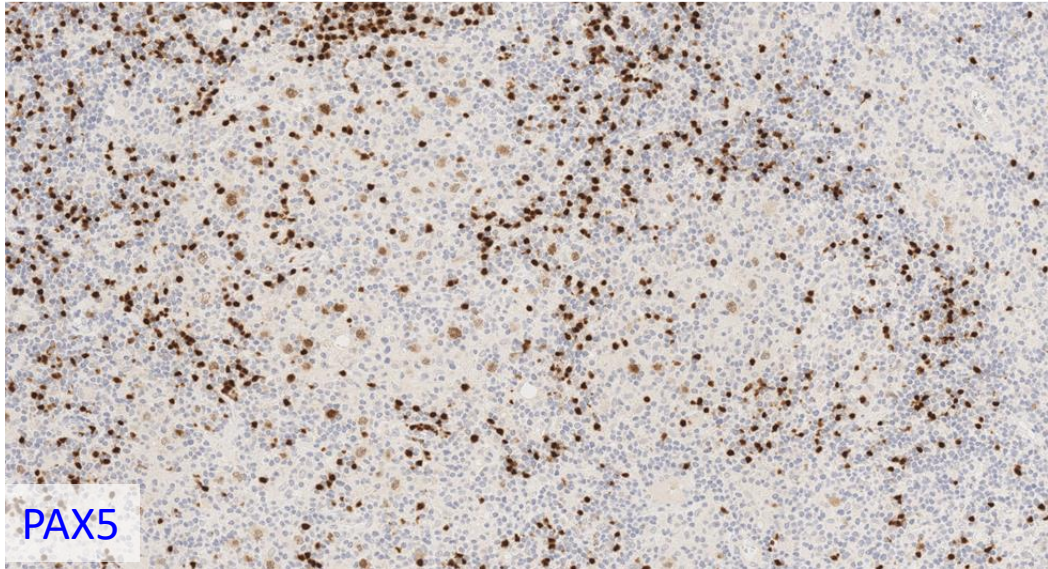


HE

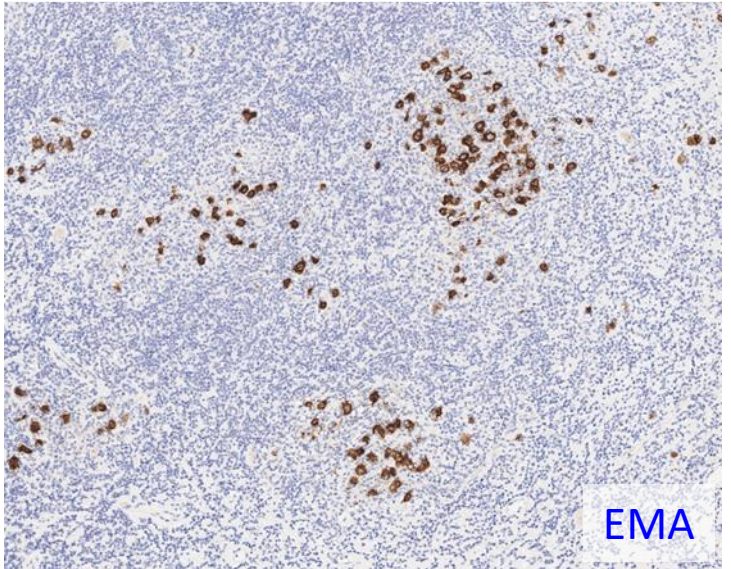


CD20

Diagnostic retenu: Lymphome de Hodgkin nodulaire à prédominance lymphocytaire dans un pattern E : « T-cell rich nodular » selon Fan (OMS 2016).



PAX5

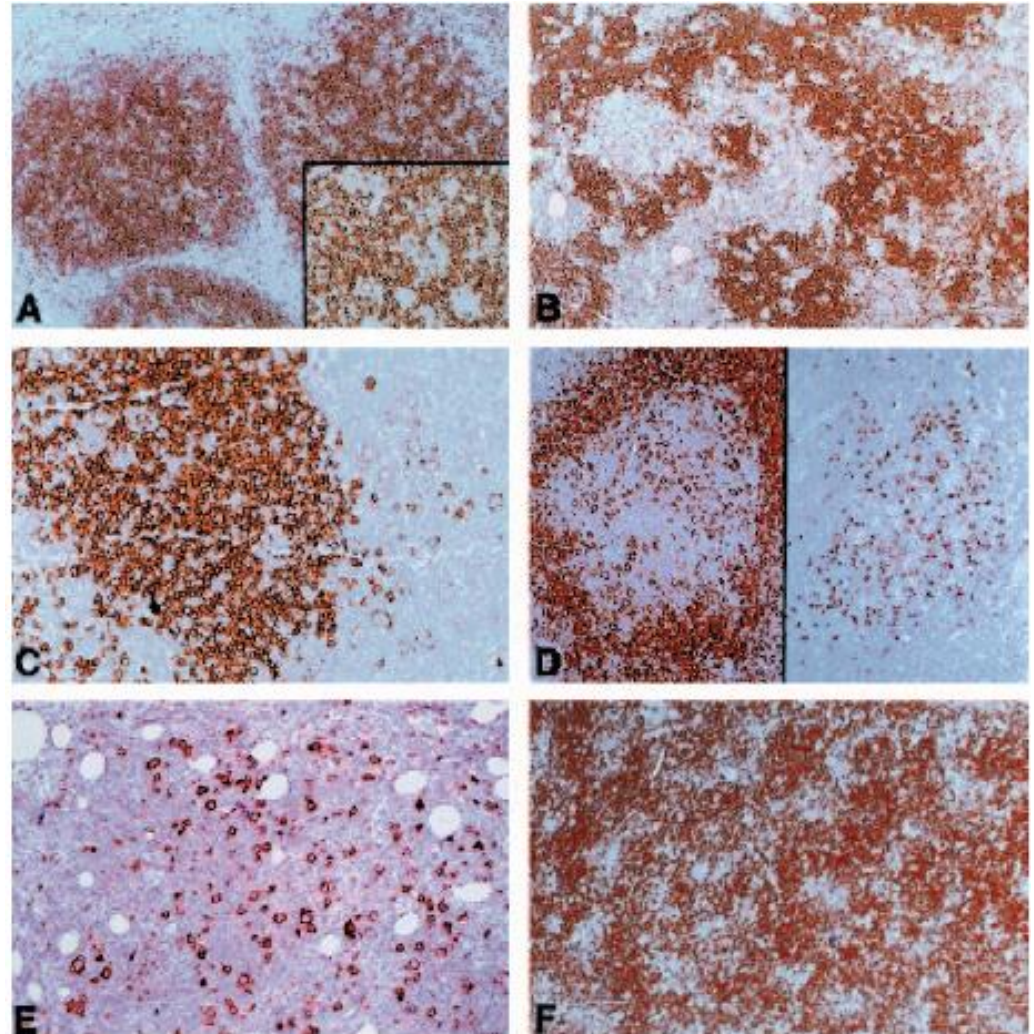
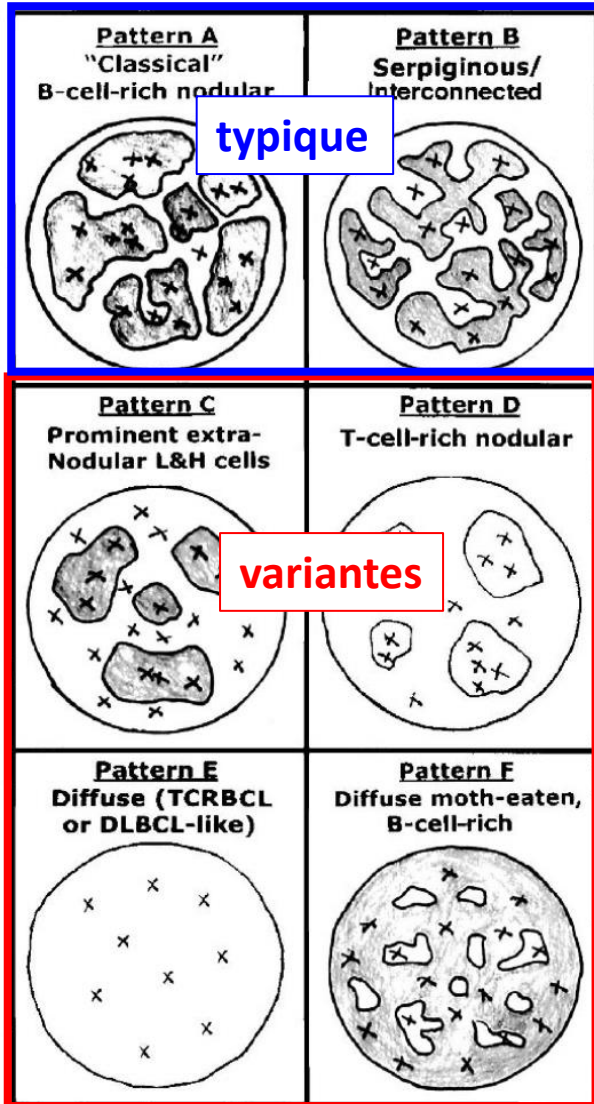


EMA

Characterization of Variant Patterns of Nodular Lymphocyte Predominant Hodgkin Lymphoma with Immunohistologic and Clinical Correlation

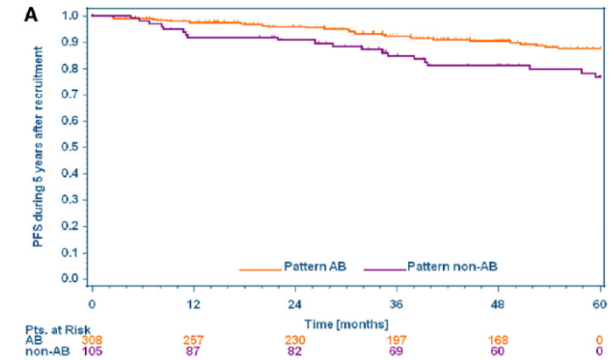
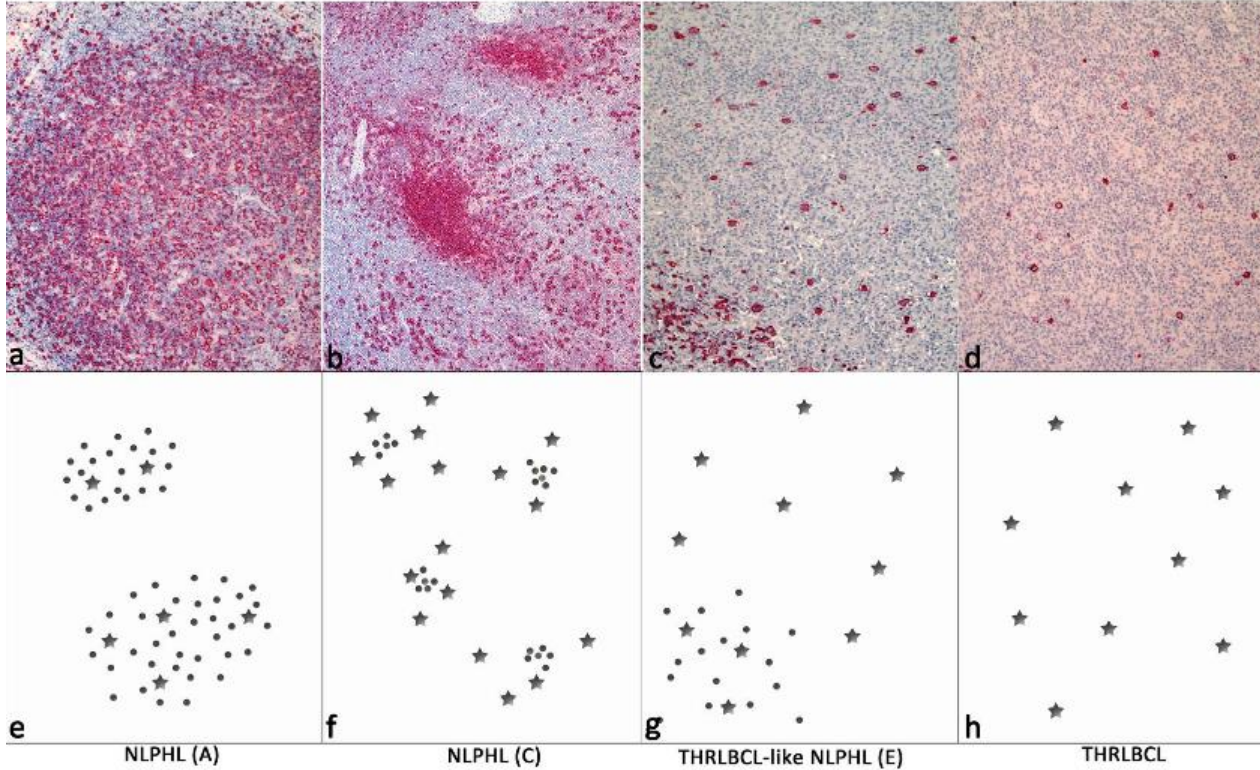
Zhen Fan, MD, Yasodha Natkunam, MD, PhD, Eric Bair, BS, MS, Robert Tibshirani, PhD, and Roger A. Warnke, MD

Fan, Am J Surg Pathol 2003



A, B, C, F: FDC meshwork, nodular

Impact pronostic des variantes histopathologiques du LHNPL



Plos One, Hartmann S et al 2013

- Les variantes histopathologiques sont associées à une **maladie plus avancée**
- La PFS à 5 ans est significativement meilleure pour les formes histologiques typiques (A,B) que pour les variantes C D E .
- Une forme histopathologique variante constitue un **risque indépendant de progression/rechute** dans les 5 ans ayant suivi l'enregistrement dans cette étude.

Blood, Hartmann S et al 2013

Pour résumer ces observations



Prolifération à grandes cellules B

Contexte clinique: âge, atcd aigu/chronique, localisation LDH PetScan (SUV)...

DLBCL-NOS

GC vs nGC/ABC
DE
FISH
+/- RT-MLPA
+/- NGS

si CD5+: faire une cycline D1 pour éliminer un l. du manteau pléomorphe à grandes cellules



diffus

PMBL

Cellules claires, fibrose
MAL, CD23, PDL1
FISH CIITA
+/- RT-MLPA, +/- NGS

nodulaire

LF3B

Marqueurs GC
CD10 BCL6
FDC: CD21, CD23

nodulaire (diffus)

LHNPL (Poppema)

LP cells
EMA, IgD, PD1
FDC: CD21, CD23



diffus

TCRBCL

Clinique: stade IV, LDH élevées...
EMA, absence de FDC et de petits lymphocytes B

Conclusion

- Sous réserve de bonnes conditions (morphologie, biopsie de bonne taille et représentative), le diagnostic de LDGCB est possible.
- Si moindre doute, en particulier si architecture nodulaire, demander une biopsie exérèse de l'adénopathie si accessible.
- Confrontation avec la clinique+++
- Intérêt des analyses moléculaires dans les cas difficiles.

Remerciements

- Pr Philippe Gaulard
- Dr Elsa Poullot
- Dr Claire Glaser
- Dr Yves Denoux
- Dr Emmanuelle Menet