

# La **DIAGNOSTICA** **EMATOPATOLOGICA** nell'ERA della **MEDICINA** di **PRECISIONE**

**Session: B cell lymphomas with germinal centre origin**

## **Clinical Case**

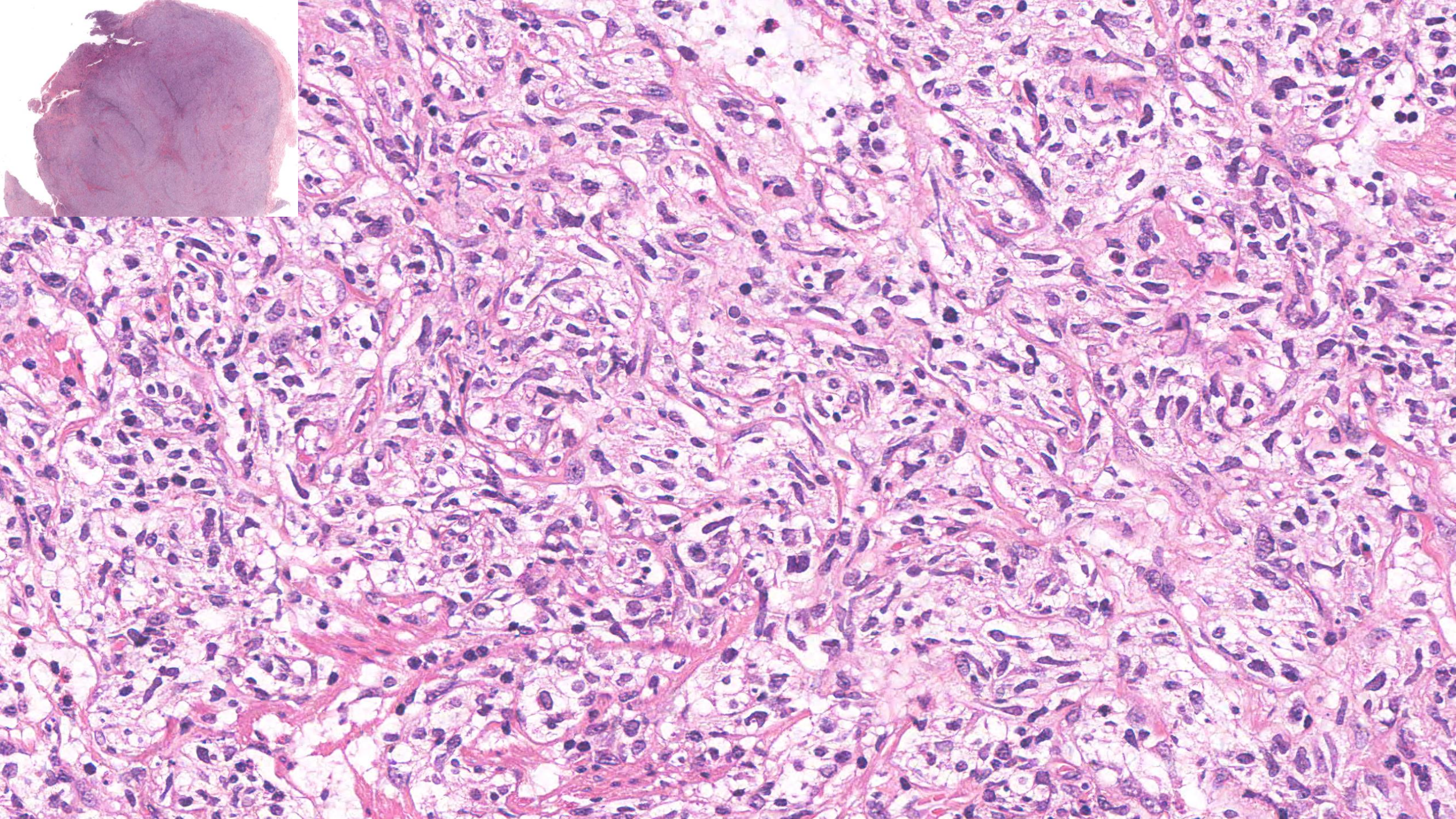
*Evelina Rogges/Prof.ssa Arianna Di Napoli*

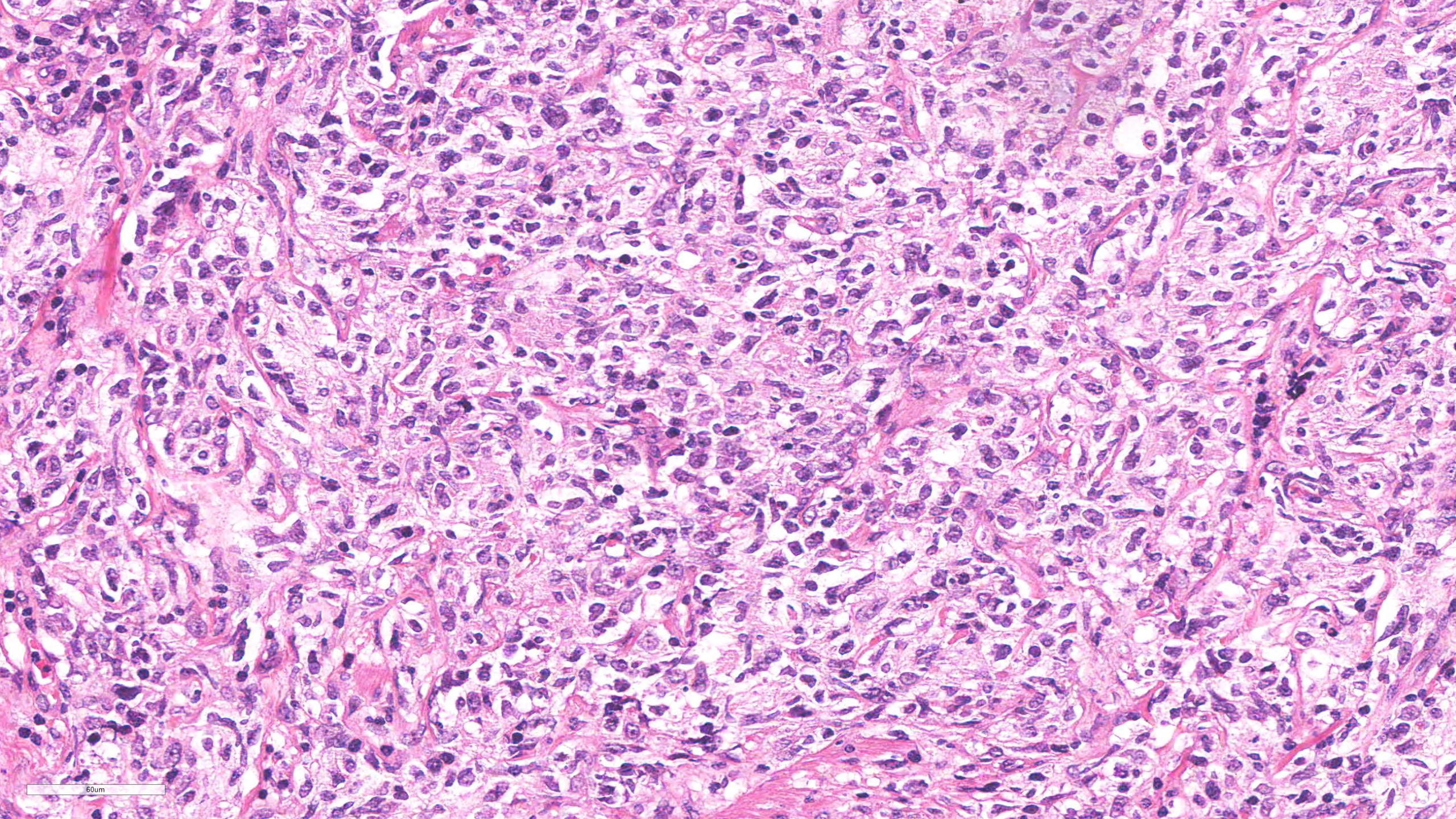
*Dipartimento di scienze medico-chirurgiche e medicina traslazionale, Sapienza  
University of Rome*

## Case history

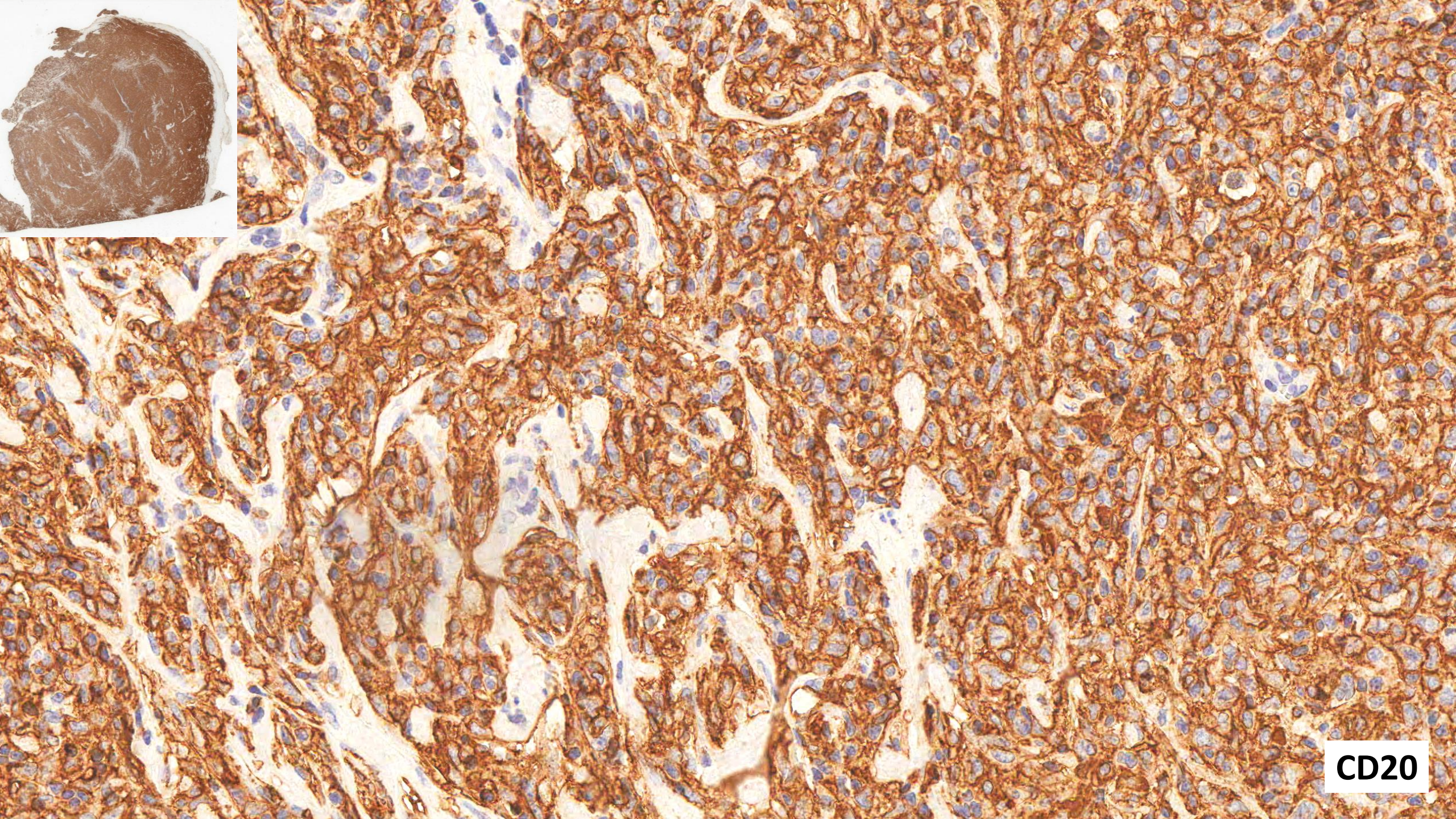


- 45-year-old female patient with a **10 cm bulky mass** involving the **vaginal walls**
- She was referred to our center for a **second opinion** after a diagnosis of **GCB-type DLBCL** according to the Hans algorithm, based on **multiple tissue fragments**

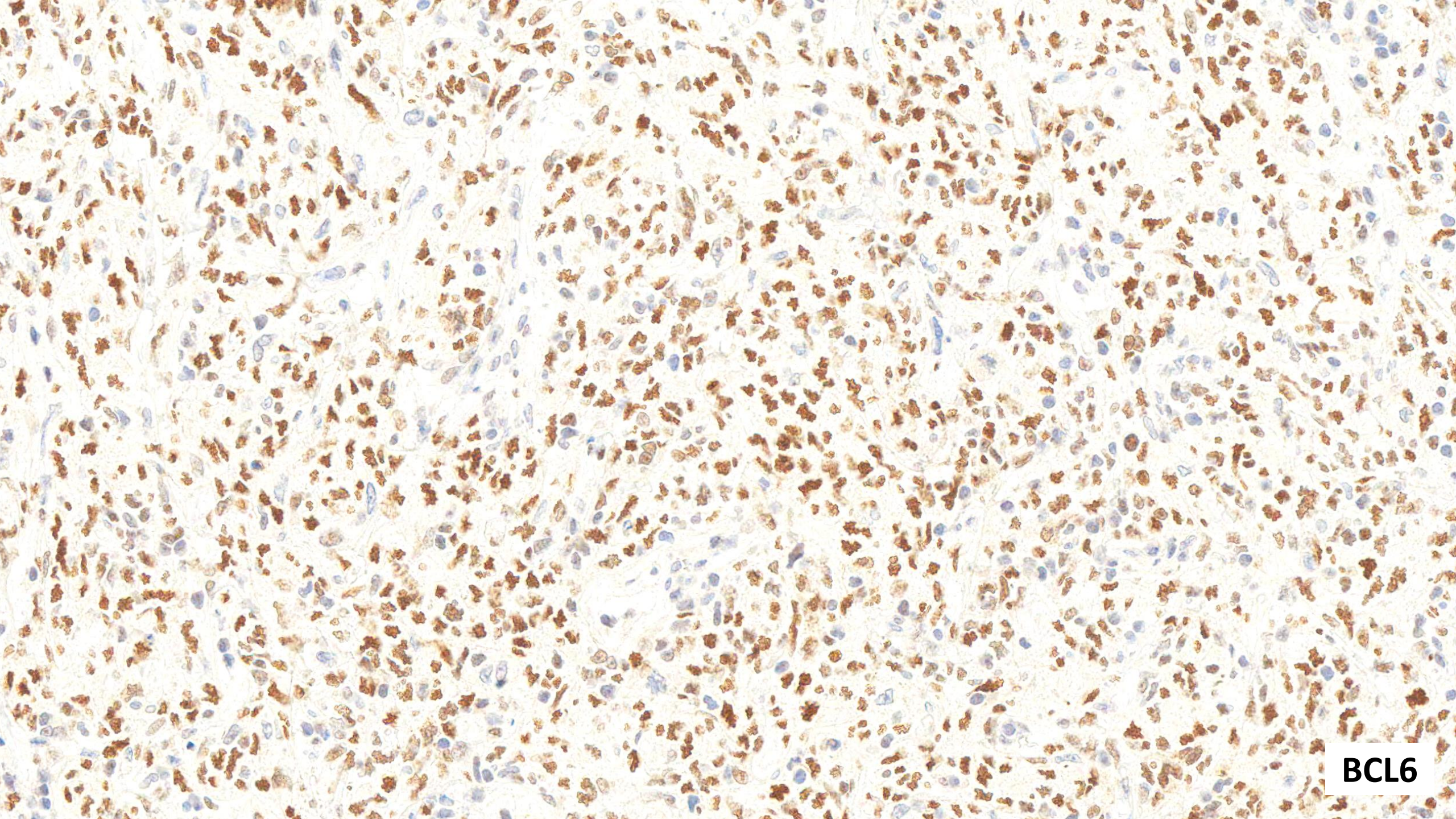




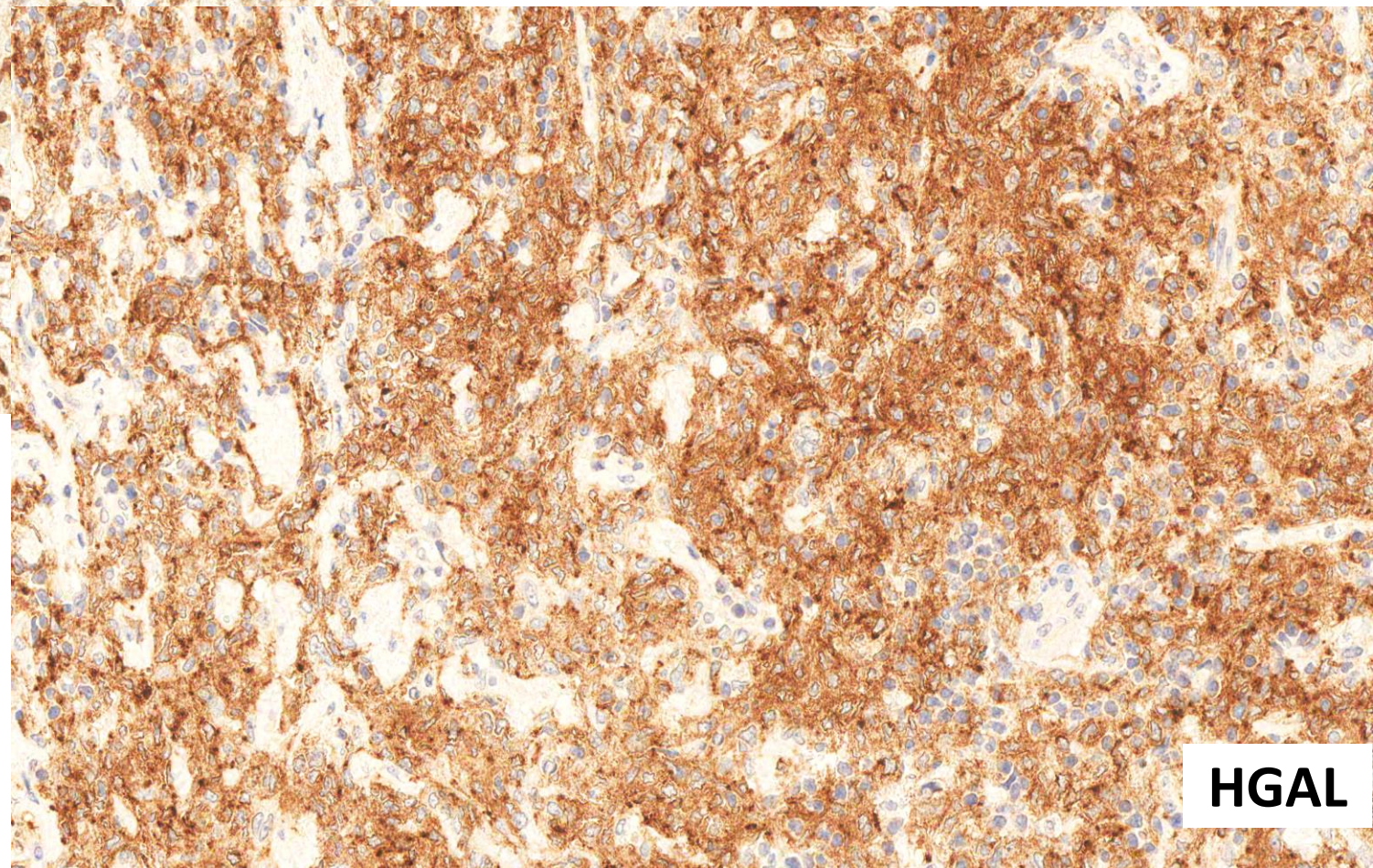
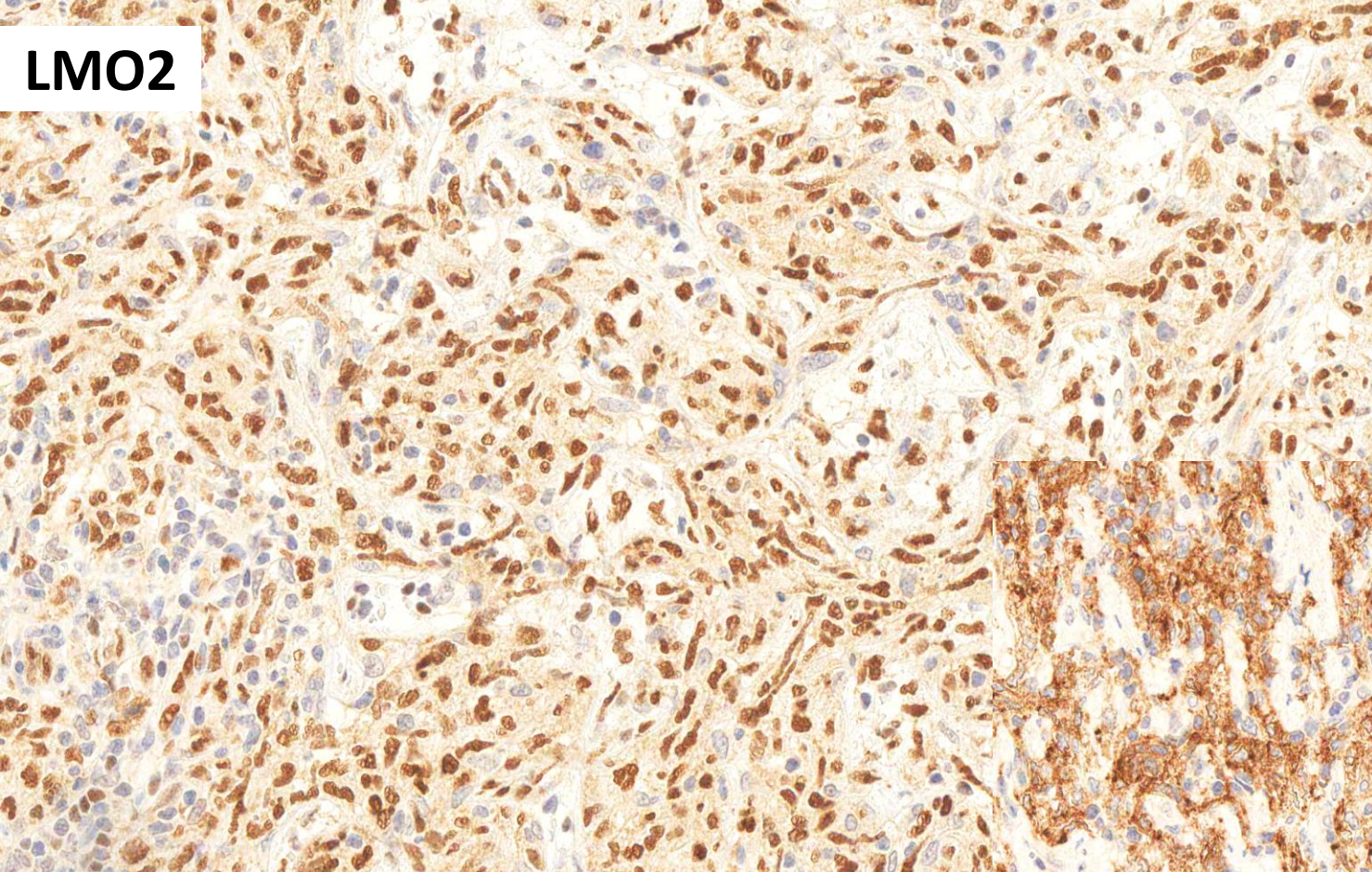
60um

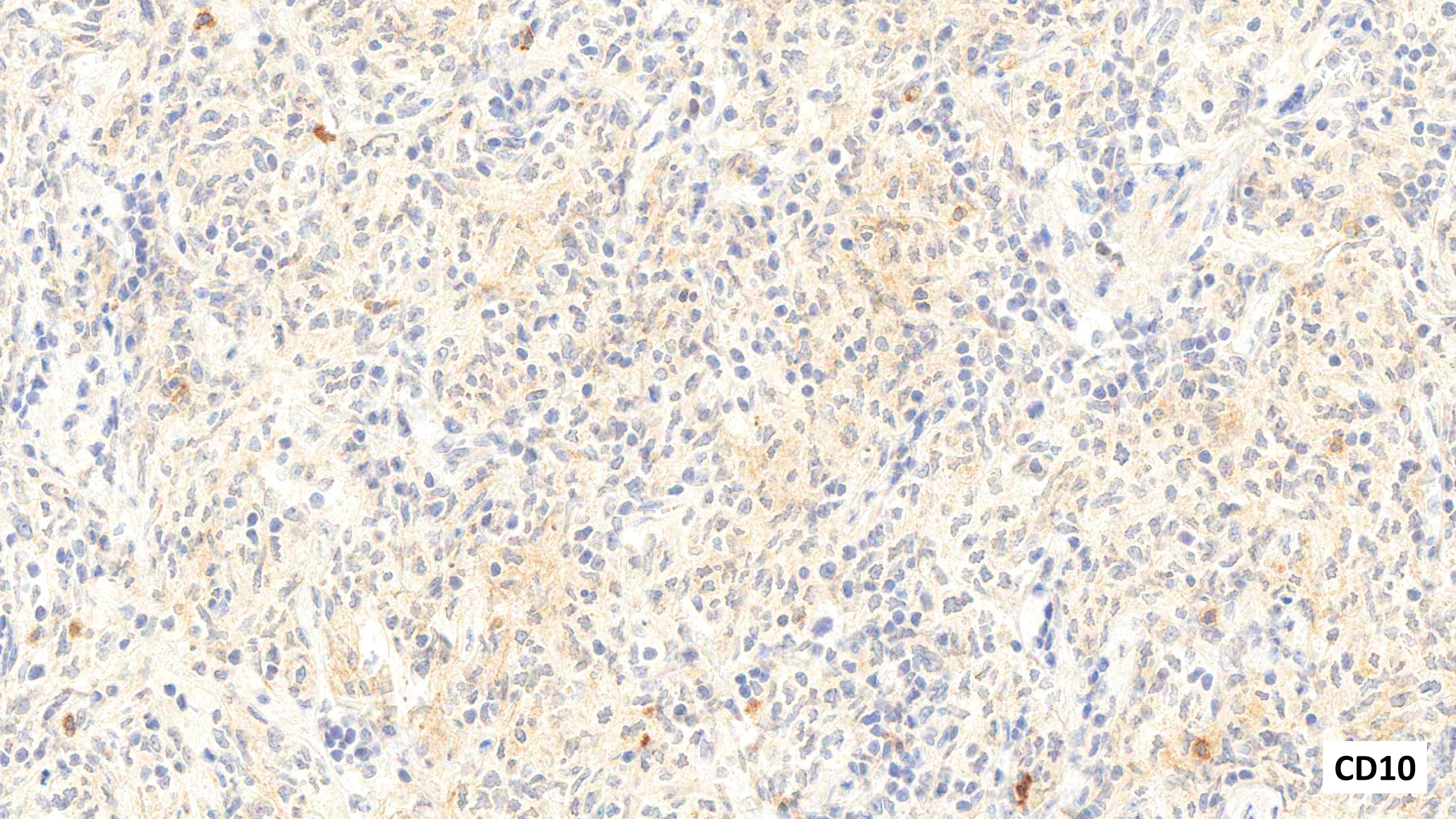


**CD20**

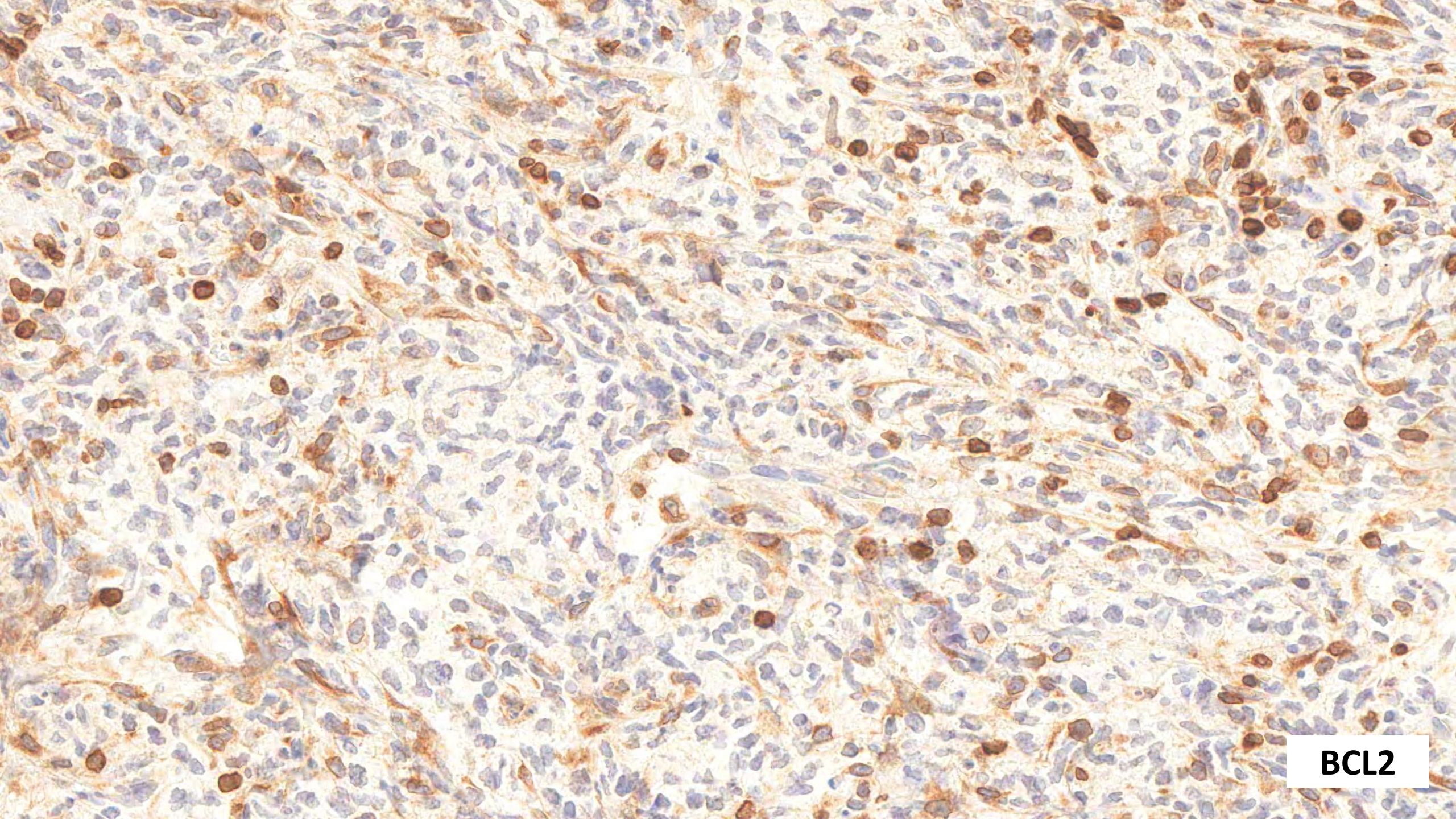


**BCL6**

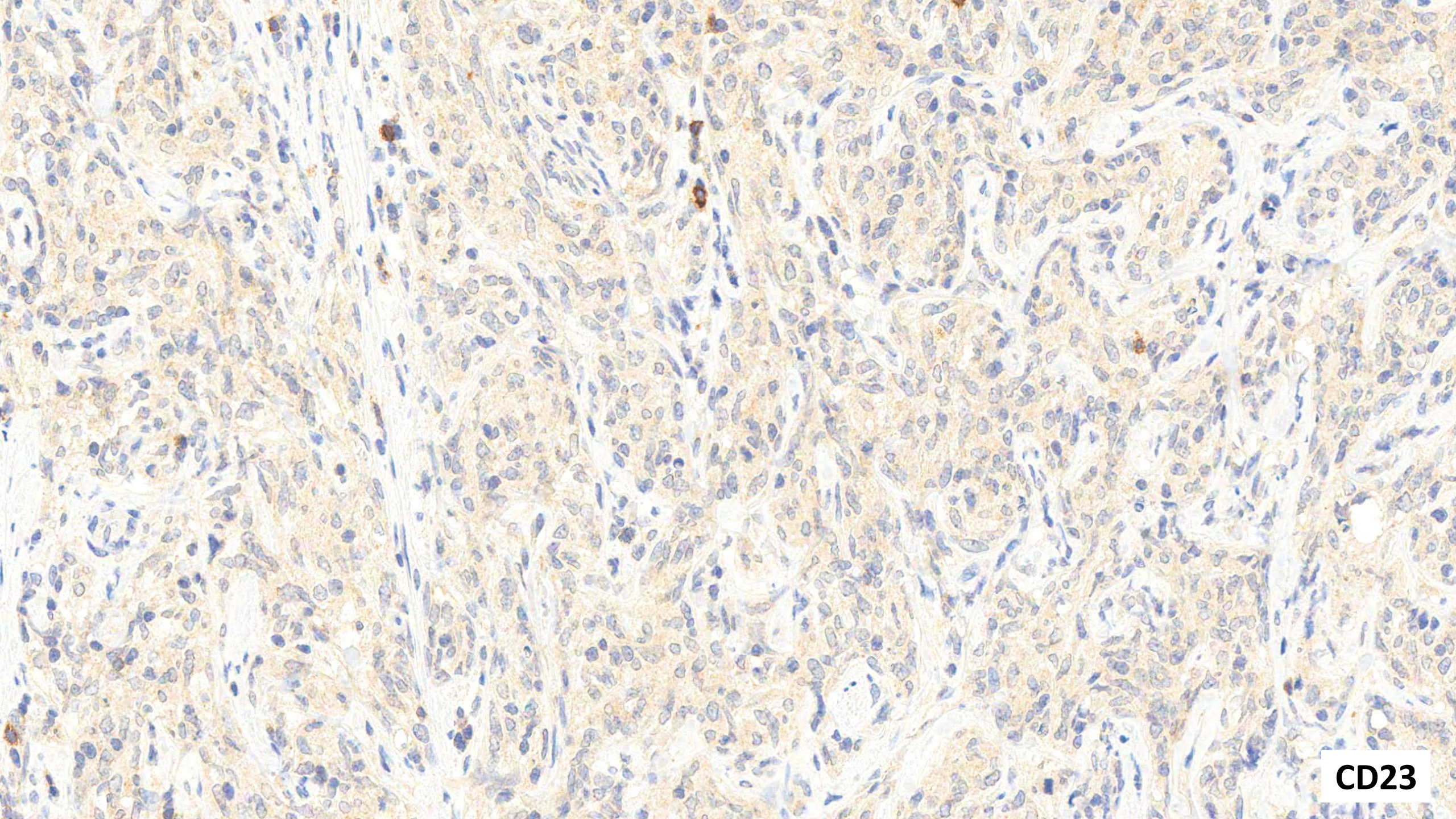




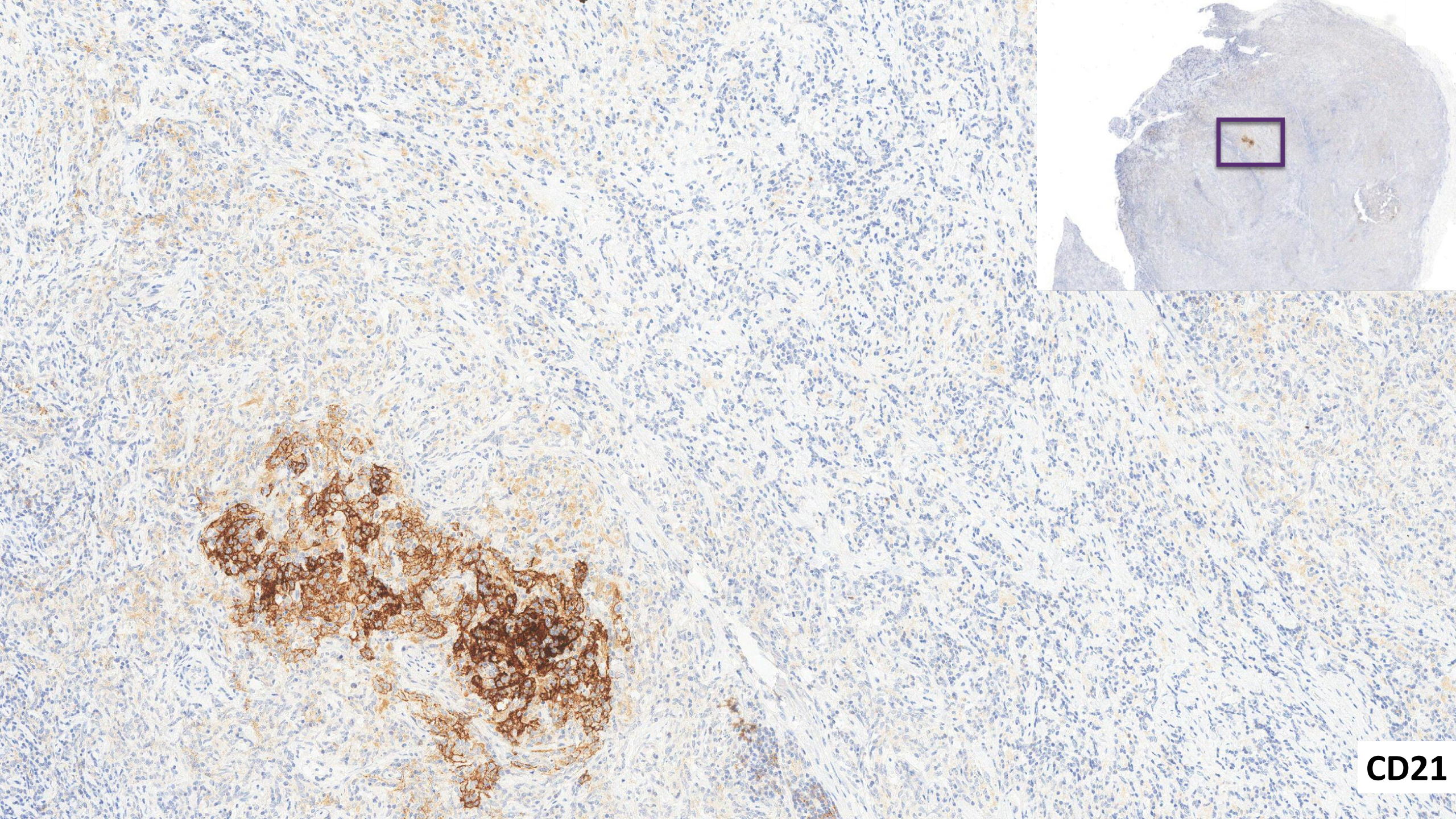
**CD10**



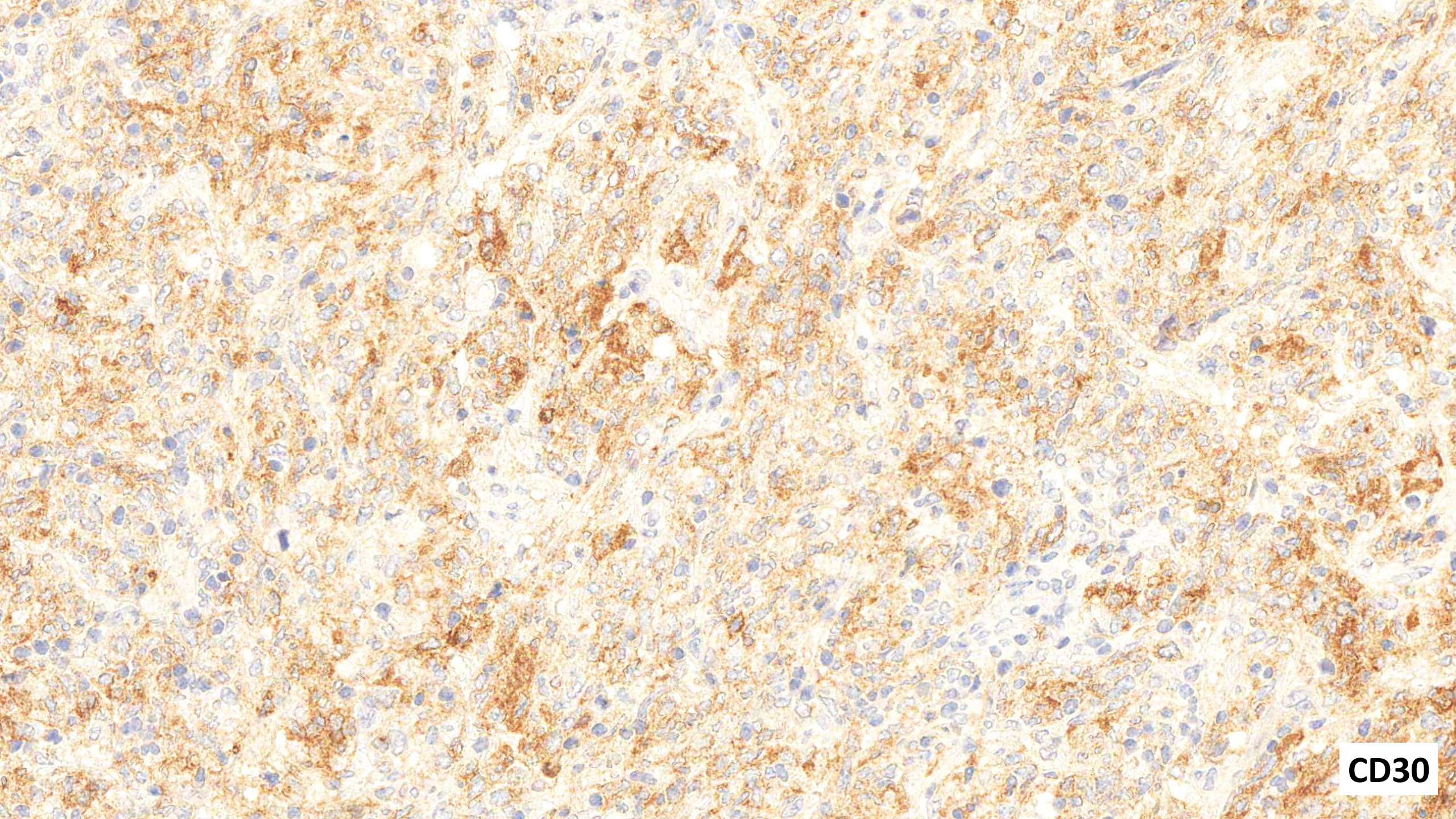
**BCL2**



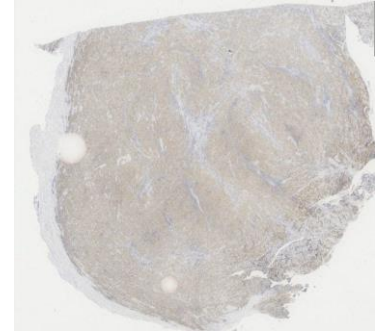
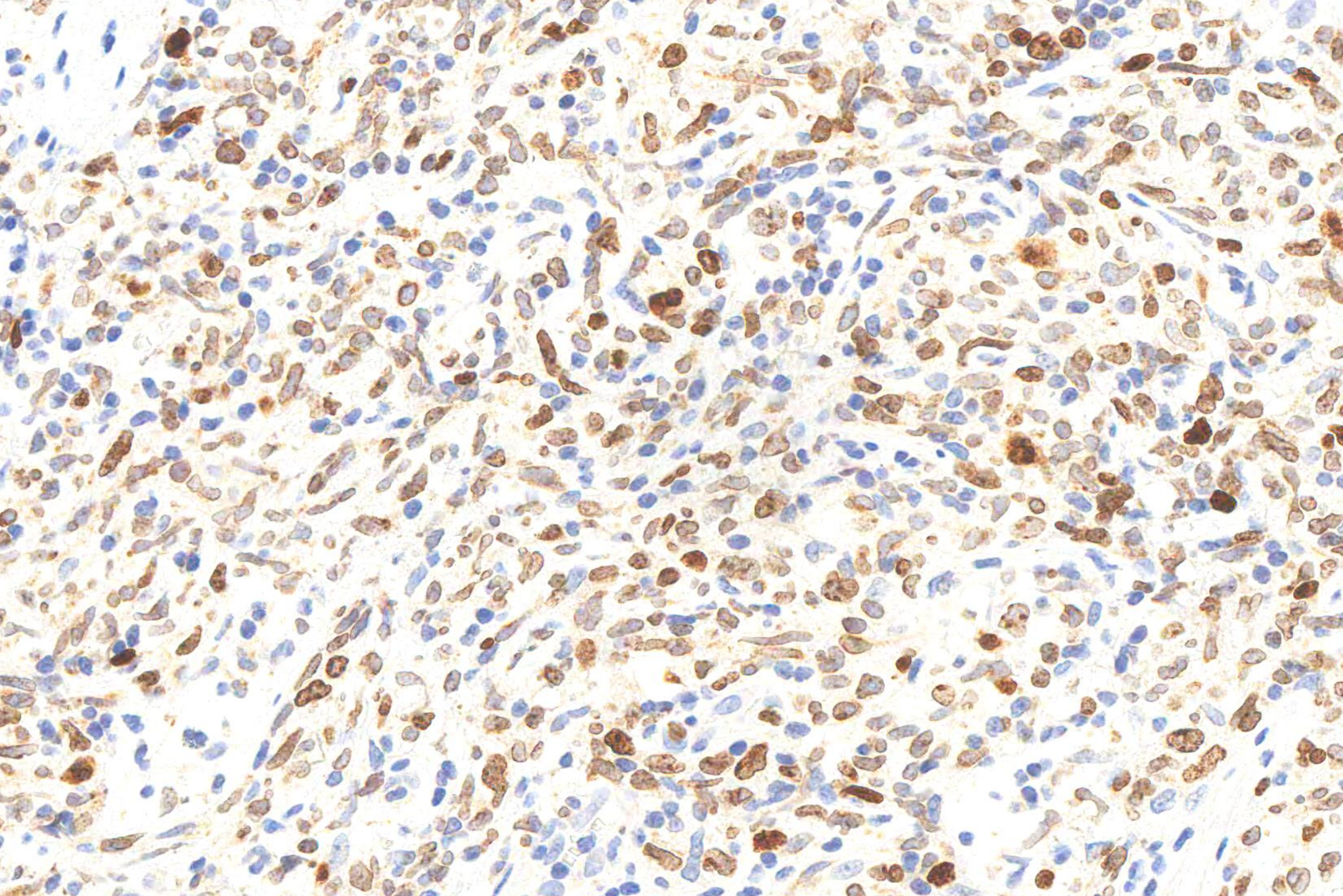
**CD23**



**CD21**

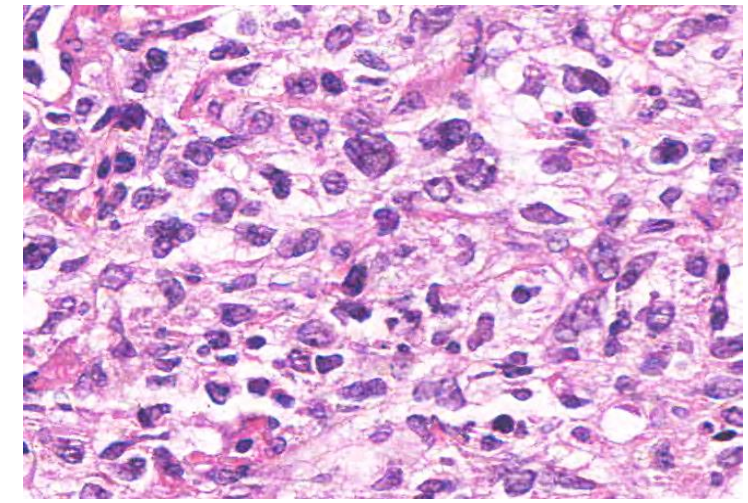
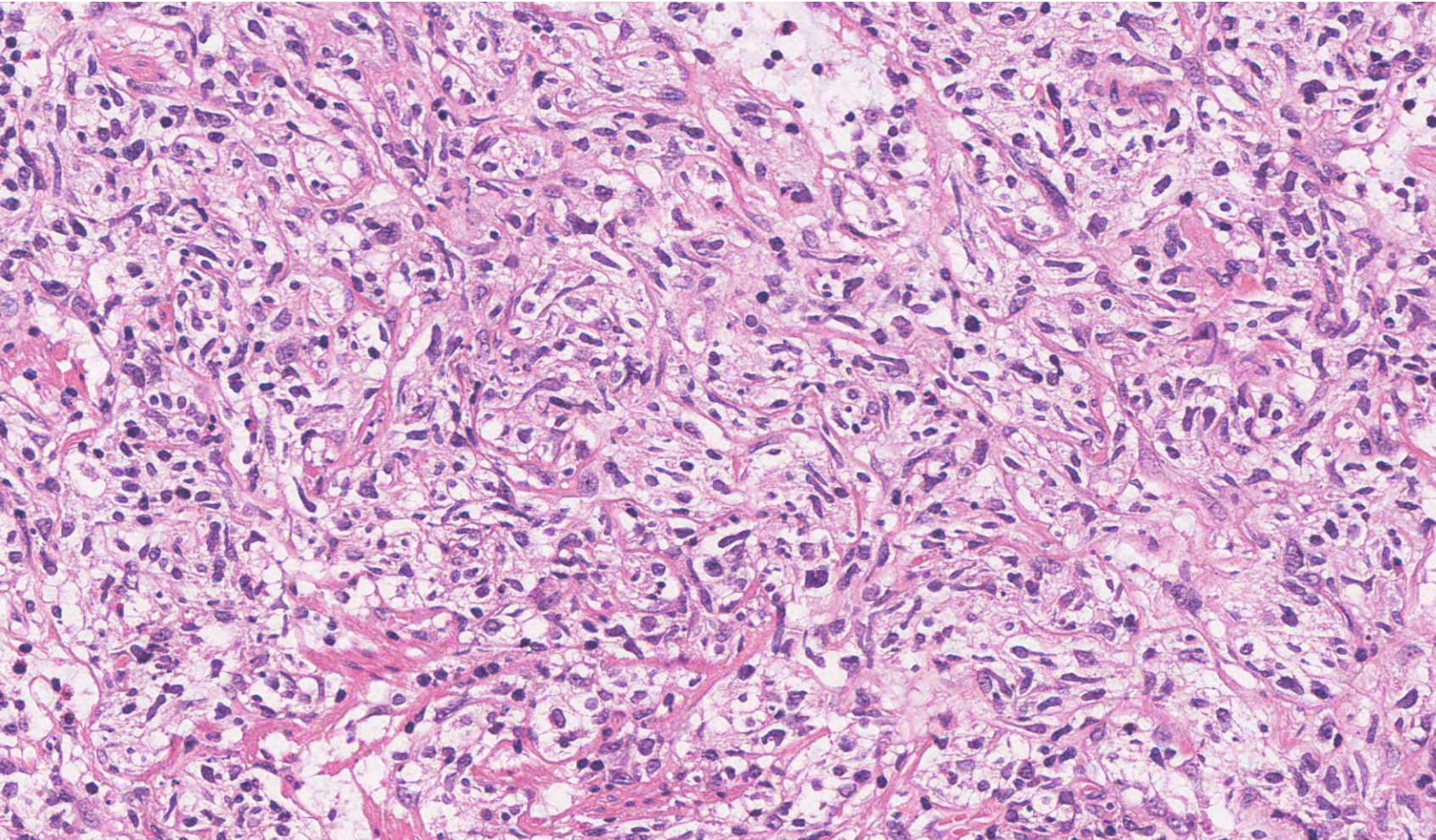


**CD30**



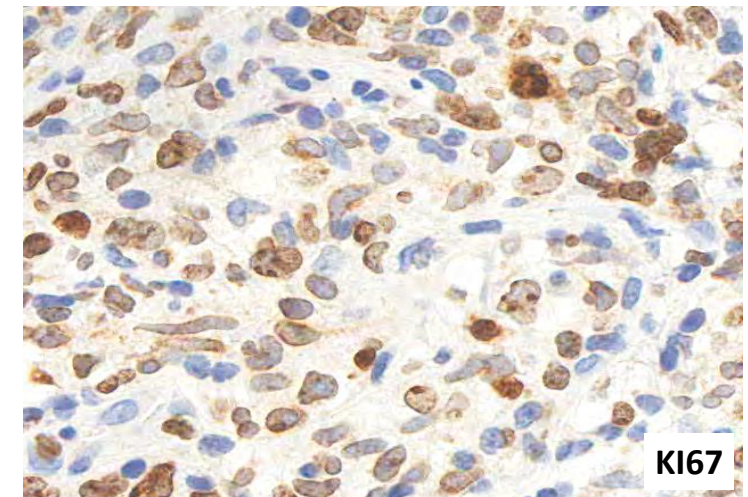
**KI67**

# Histological features



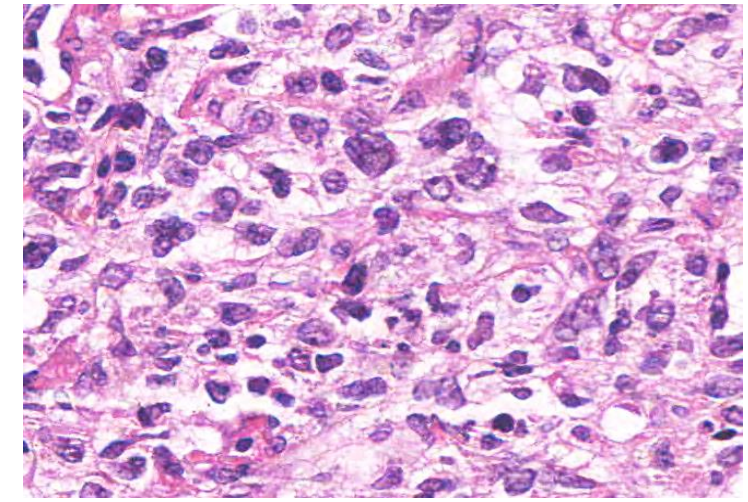
Extranodal B cell lymphoma with diffuse growth pattern

Large centrocytes and centroblasts with some spindle-shaped cells



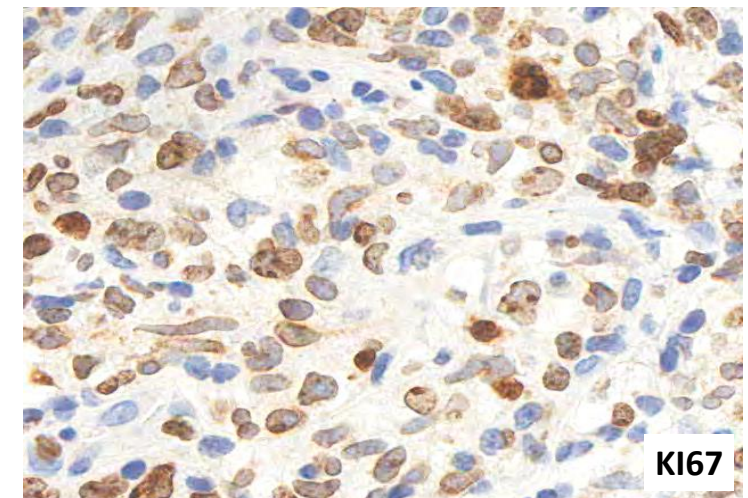
Immunophenotype	
CD20	+
CD79a	+
CD10	-/+ weak
BCL6	+
HGAL	+
LMO2	+
BCL2	-/+ focal and weak
MUM1	-
CD23	-
CyclinD1	-
CD5	-
CD3	-
CD30	+/-
CD15	-
EBER	-
CD138	-
p53	-
MYC	-

Centrofollicular  
immunophenotype



Extranodal B cell lymphoma with  
diffuse growth pattern

Large centrocytes and centroblasts  
with some spindle-shaped cells

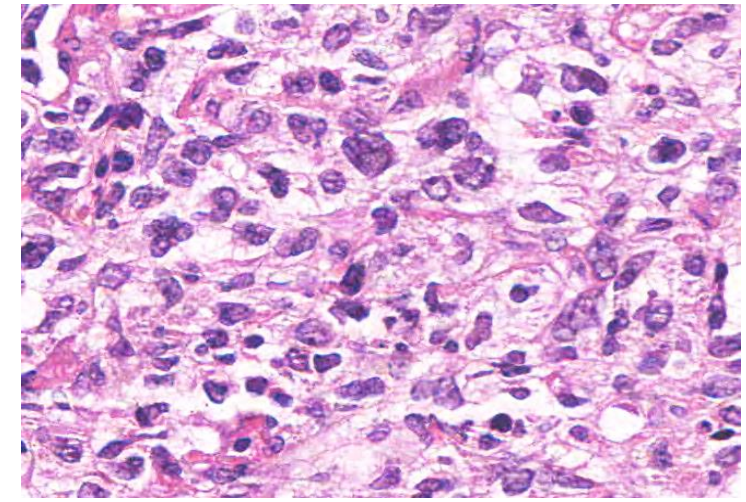


Ki67

Immunophenotype	
CD20	+
CD79a	+
CD10	-/+ weak
BCL6	+
HGAL	+
LMO2	+
BCL2	-/+ focal and weak
MUM1	-
CD23	-
CyclinD1	-
CD5	-
CD3	-
CD30	+/-
CD15	-
EBER	-
CD138	-
p53	-
MYC	-

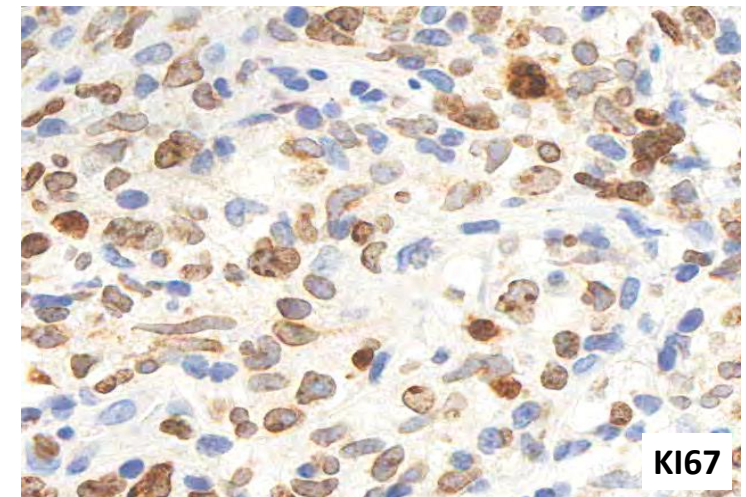
Centrofollicular  
immunophenotype

Focal and faint BCL2  
staining, MUM1-, CD23-



Extranodal B cell lymphoma with  
diffuse growth pattern

Large centrocytes and centroblasts  
with some spindle-shaped cells



KI67

# WHO and ICC classification of Follicular lymphoma

International Agency for Research on Cancer



## B-cell lymphoid proliferations and lymphomas

### Mature B-cell neoplasms

#### *Follicular lymphoma*

Follicular lymphoma: Introduction

In situ follicular B-cell neoplasm

Follicular lymphoma

Paediatric-type follicular lymphoma

Duodenal-type follicular lymphoma

#### *Cutaneous follicle centre lymphoma*

Primary cutaneous follicle centre lymphoma



The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee

#### Follicular lymphoma

In situ follicular neoplasia

Duodenal-type follicular lymphoma

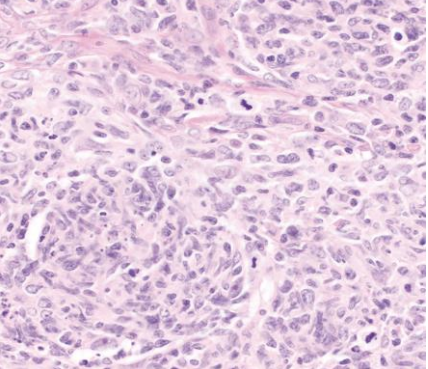
*BCL2-R-negative, CD23-positive follicle center lymphoma*

Primary cutaneous follicle center lymphoma

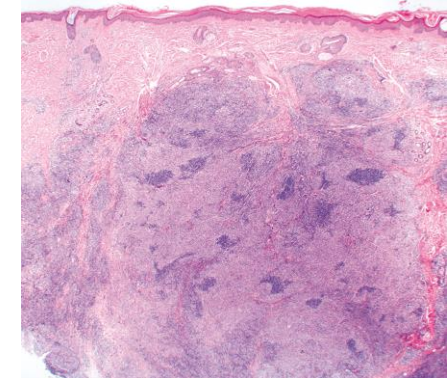
Pediatric-type follicular lymphoma

Testicular follicular lymphoma\*

Large B-cell lymphoma with *IRF4* rearrangement\*



# PCFCL



**Localized** skin lesions with a **follicular, follicular and diffuse, or diffuse growth pattern**

**Large centrocytes (may be spindle-shaped)** with variable numbers of **centroblasts**

**BCL6+**, **CD10** is **generally negative** in cases with a diffuse growth pattern

Most cases **BCL2-** or show faint BCL2 staining, most cases are **BCL2R-**

**PCFCL with a diffuse growth pattern, previously often classified as DLBCL, should be differentiated from PCDLBCL, LT**

**Excellent prognosis** irrespective of the clinical, histological, and the genetic aberrations (5-year survival rate > 95%)

Mutations in **TNFRSF14**, **SOCS1**, **STAT6**, **TNFAIP3**, **FOXO1**, **with significantly lower mutations in CREBBP, KMT2D, EP300, than cFL**

## **Follicle Center Lymphoma (FCL) of the Lower Female Genital Tract (LFGT): A Novel Variant of Primary Cutaneous Follicle Center Lymphoma (PCFCL)**

Annapurna Saksena<sup>1</sup>, Ashish Jain<sup>2 3</sup>, Svetlana D Pack<sup>1</sup>, Jung Kim<sup>1</sup>, Ina Lee<sup>1</sup>, Manoj Tyagi<sup>1</sup>, Liqiang Xi<sup>1</sup>, Stefania Pittaluga<sup>1</sup>, Mark Raffeld<sup>1</sup>, Elaine S Jaffe<sup>1</sup>

**15 cases** (2000-2022), median age of 41 years (range 31-53)

**60%** presented with symptomatic mass lesions, with **bulky disease**

**Follicular component 80%** cases, **purely diffuse pattern 20%** cases

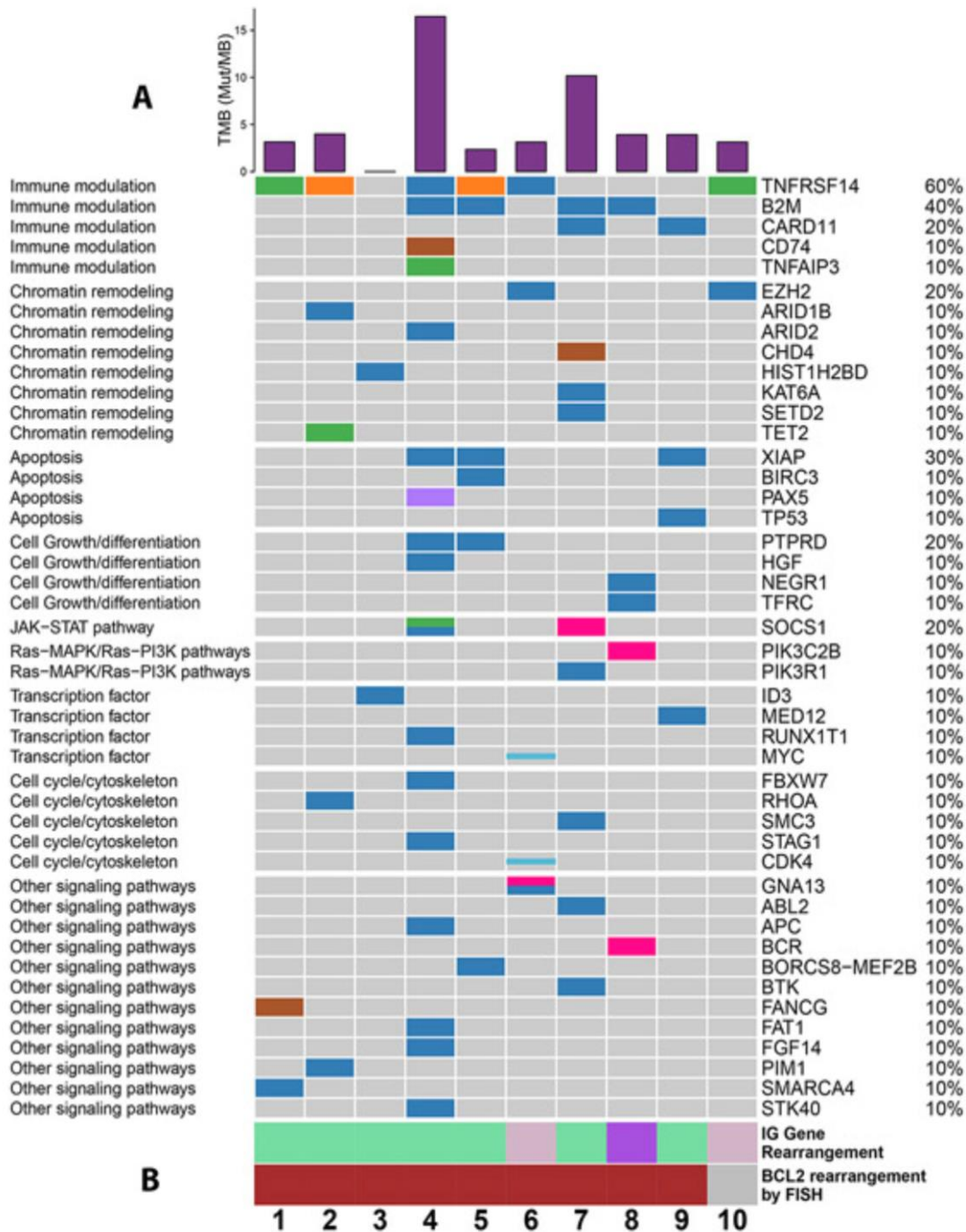
**Large centrocytes and centroblasts** were a **prominent feature leading to concern for DLBCL (60% diagnosed as DLBCL)**

BCL-6+ in all cases, CD10 was positive 29% cases and 87% were BCL-2 negative

**83% in CR following treatment (60% of patients** with available treatment strategy received combination CHT)

5-year overall survival 100%, 5-year relapse-free survival was 76%

# FISH and Molecular features



Mutations (10 cases TSO500 )

TNFRSF14 (60%)

B2M and XIAP (40 e 30%)

EZH2 e SOCS1 (20% each)

No CREBBP e KMT2D

FISH

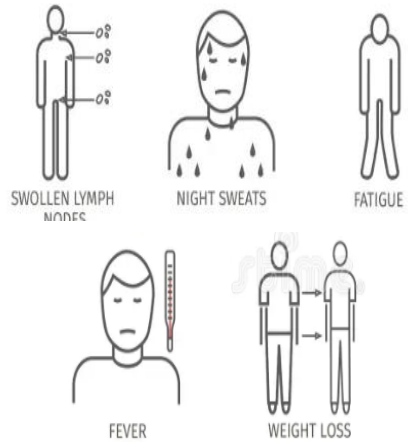
3/12 BCL6R

1/11 BCL2R

# Clinical Data

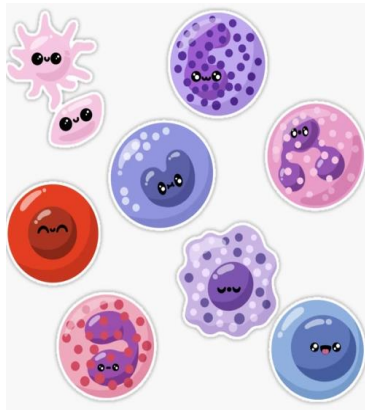


## Symptoms



No B symptoms

## Laboratory findings



No laboratory abnormalities

## PET/CT



Single site disease,  
SUVmax 18

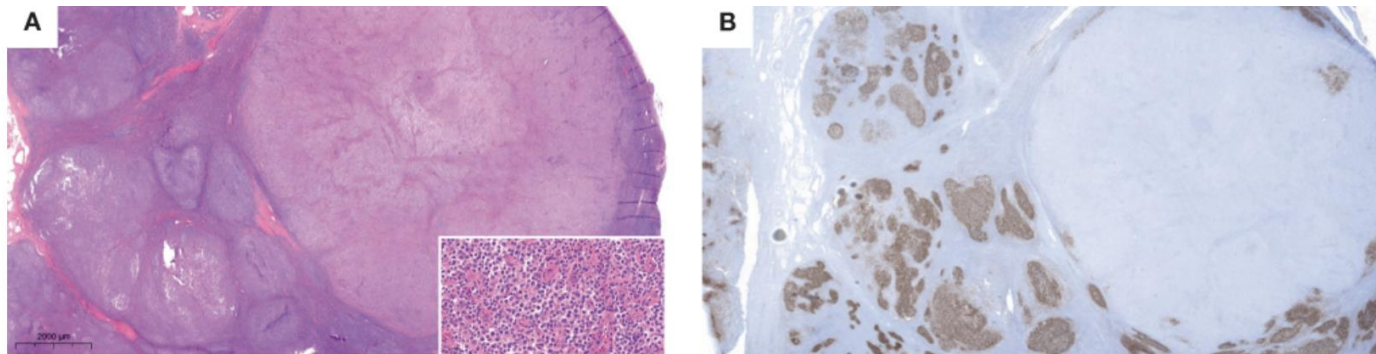
*FCL-LFGT* is not currently recognized as a distinct entity, given the vaginal rather than cutaneous location, a diagnosis of **primary cutaneous follicle center lymphoma** was not applicable

From the clinical standpoint, the high FDG uptake, and the incomplete excision of the bulky mass was considered to warrant treatment

Rare cases of FL with a prominent diffuse pattern and an increased number of centroblasts (consistent with FL3A) have been reported, and such cases were designated as DLBCL in the previous (revised fourth) edition { 27117536 }. Currently, it is uncertain whether such cases should be classified as FL or DLBCL. In such cases, individual treatment choices should be made in multidisciplinary conference settings, taking into consideration clinical, laboratory, and imaging parameters. However, the presence of diffuse areas composed entirely or predominantly of large cells warrants a diagnosis of DLBCL.



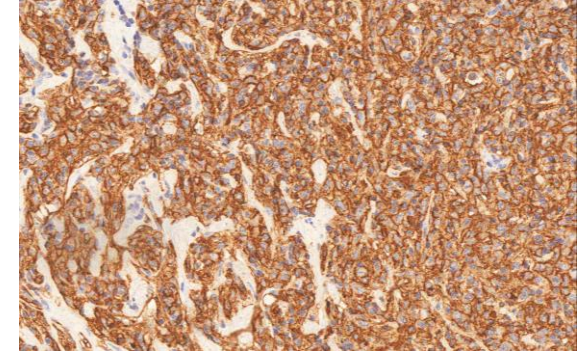
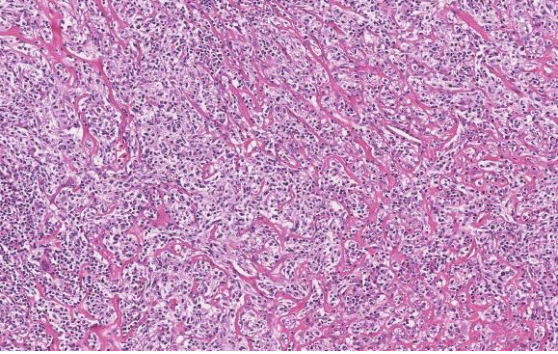
The International Consensus Classification of Mature Lymphoid Neoplasms: a report from the Clinical Advisory Committee



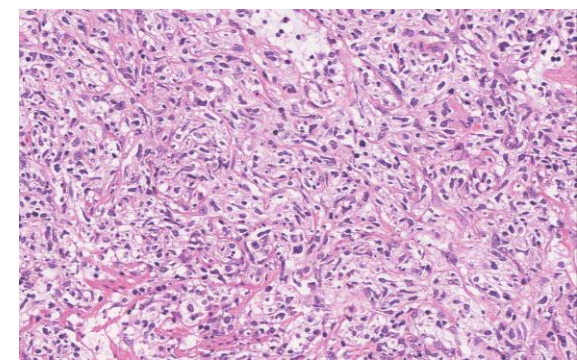
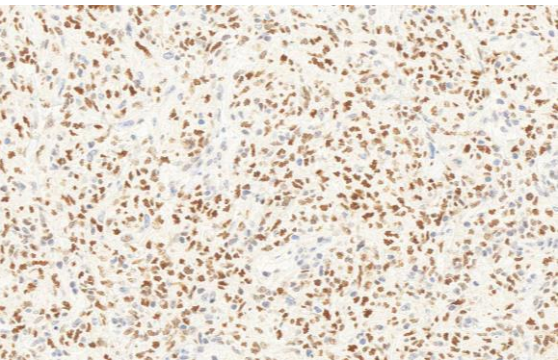
**FIGURE 57.5** Lymph node infiltrated by follicular lymphoma (FL) with a component of diffuse large B-cell lymphoma (DLBCL). **A:** This lymph node shows two different areas. On the left side there is infiltration by neoplastic follicles without mantle zones. The infiltrate is composed of admixed centrocytes and centroblasts corresponding to FL grade1-2. The second area on the right side shows a diffuse area composed of sheets of large cells consistent with DLBCL (inset: high magnification showing diffuse proliferation of large centrocytes and centroblasts). **B:** CD21 staining shows follicular dendritic cell meshworks in the follicular areas but not in the DLBCL.

Diffuse FL diagnosis should be made with caution after excluding other lymphomas, especially DLBCL in case of predominant large B-cell proliferation

## Diagnosi



«The observed morphological and immunophenotypic features, together with the clinical finding of a single disease site, appear similar to those of primary cutaneous follicle center lymphoma with diffuse growth pattern (Saksena A. et al., “Follicle Center Lymphoma (FCL) of the Lower Female Genital Tract (LFGT): A Novel Variant of Primary Cutaneous Follicle Center Lymphoma (PCFCL).” Am J Surg Pathol. 2023). However, given the non-cutaneous site, and the absence of a defined category for FCL-LFGT the neoplasm currently appears classifiable as DLBCL, GCB type based on the Hans algorithm»



# Molecular findings in our case

## Targeted NGS 60 genes

Genes	Variant Effect	VAF	Coding	ClinVar	COSMIC	dbSNP	Domain	In silico predictor	Franklin
EZH2	missense	19.30	p.Tyr646Phe	Likely pathogenic	COSV57445929 (DLBCL, FL)	rs267601394	SET	pathogenic	TIER1/LP
SOCS1	frameshift	17.89	p.Gln131ProfsTer69	NR	NR	NR	SH2	NA	TIER 3/VUS

Absence of *BCL2*, *MYC* e *BCL6* genes rearrangements

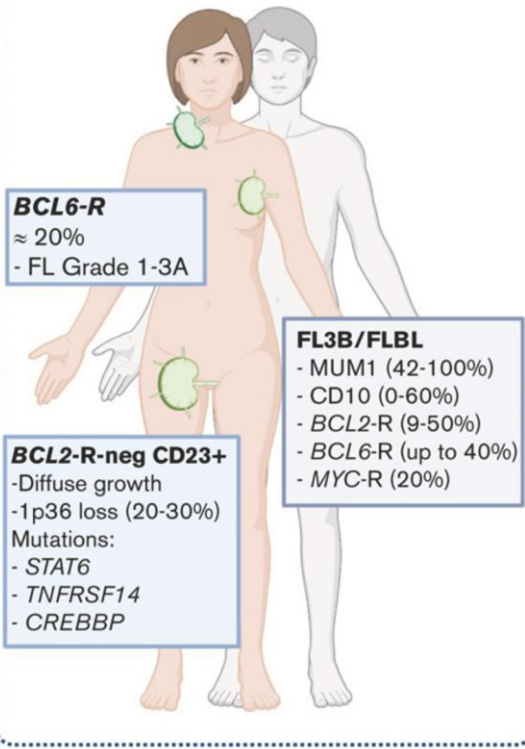
R-CHOP without maintenance therapy

# The clinical and molecular taxonomy of t(14;18)-negative follicular lymphomas

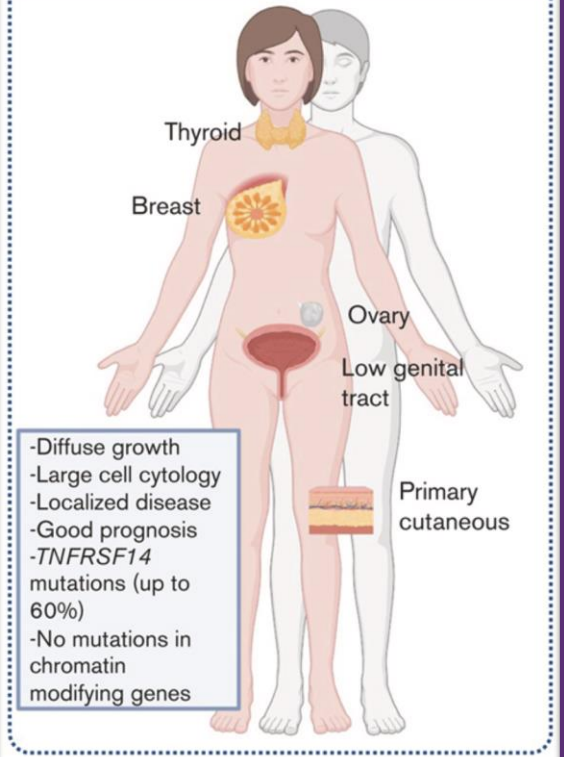
Itziar Salaverria, Oliver Weigert, Leticia Quintanilla-Martinez

The new classifications acknowledge that knowing the **translocation status** will fill a **critical knowledge gap**, including **diagnostic refinement** and, potentially, **patient stratification in the near future**

## Nodal presentation



## Extranodal presentation



## Nodal lymphomas

- t(14;18)-negative follicular lymphoma
- BCL2-R negative, CD23+ FCL
  - FL grade 1-3A with BCL6-R
  - Others
- FL grade 3B

## Extranodal lymphomas

- Primary cutaneous follicle center lymphomas
- Other extranodal primary FL

## Acknowledgement

### Reparto di Istopatologia Ospedale Sant'Andrea, Roma

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Università Sapienza Roma

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Istituti fisioterapici ospedalieri (IFO)

**Dr. Enzo Gallo**  
Istituti fisioterapici ospedalieri (IFO)

### Reparto di Ematologia Policlinico Umberto I, Roma

**Prof.ssa Alice Di Rocco**  
Università Sapienza Roma

**Dr. Luigi Petrucci**  
Università Sapienza Roma

# The clinical and molecular taxonomy of t(14;18)-negative follicular lymphomas

Itziar Salaverria, Oliver Weigert, Leticia Quintanilla-Martinez

Entity	<i>BCL2</i> -pos FL	DNFL	Nodal <i>BCL2</i> -neg FL all	<i>STAT6</i> mut + <i>BCL2</i> -neg FL	<i>STAT6</i> mut- <i>BCL2</i> -neg FL	PCFCL <i>BCL2</i> -neg FL	LFGT FL	Thyroid <i>BCL2</i> -neg FL	PTFL	LBCL- <i>IRF4</i>
No. cases	n = 100	n = 31	n = 74	n = 52	n = 22	n = 31	n = 10	n = 4	n = 81	n = 17
<i>STAT6</i>	12	3	70	100	0	10	n.a.	n.a.	4	0
<i>KMT2D</i>	82	52	36	42	23	10	0	25	9	6
<i>CREBBP</i>	64	68	62	71	41	13	0	25	3	0
<i>TNFRSF14</i>	35	32	45	50	33	26	60	75	42	0
<i>EZH2</i>	20	16	22	23	18	7	20	0	4	0
<i>MEF2B</i>	18	16	3	4	0	0	0	n.a.	0	0
<i>HIST1H1E</i>	17	0	11	13	5	4	n.a.	n.a.	8	0
<i>TNFAIP3</i>	11	0	5	4	9	12	10	0	4	0
<i>EP300</i>	10	3	8	10	5	14	0	0	4	0
<i>FOXO1</i>	10	6	20	21	18	7	0	0	3	0
<i>SOCS1</i>	8	n.a.	12	13	9	11	20	0	11	0
<i>MAP2K1</i>	0	n.a.	0	0	0	0	0	0	44	12
<i>IRF8</i>	10	6	14	12	33	4	n.a.	n.a.	23	0
<i>IRF4</i>	0	0	3	4	0	8	0	n.a.	0	76

Age (years)	Site	Clinical presentation	Diagnostic procedure	Submitting diagnosis	Treatment (Rx)	Rx response	Outcome	Follow-up time (years)
44	C	menorrhagia	vaginal hysterectomy	DLBCL	Hysterectomy & observation	CR	Alive, NED	0.85
43	C	mass lesion	total hysterectomy	Low-grade B cell lymphoma, NOS	NA	NA	NA	NA
44	V	mass lesion	vaginal biopsy	FL grade 3 A	RICE x 3 & consolidative RT	CR	Alive, NED	4.2
40	C & V	mass lesion, pelvic pain, bleeding	endocervix, endometrium, cervix, vagina biopsy	DLBCL	R-CHOP x 6 & pelvic radiation	CR/RI	Alive, local recurrence by imaging only	4.5
36	C	routine screening	endocervix curettage, cervix LEEP	DLBCL	LEEP & R (single agent)	CR	Alive, NED	4.8
36	C & V	pelvic pain, abnormal bleeding, dyspareunia	simple hysterectomy	DLBCL	Hysterectomy & observation	CR	Alive, NED	6.9
31	C & V	mass lesion, abnormal bleeding	cervix biopsy	FL grade 2	DA-EPOCH-R x 6 cycles	CR	Alive, NED	9.2
48	C	gynecological symptoms	hysterectomy	DLBCL	Hysterectomy & observation	CR	Alive, NED	17
36	V	mass lesion	vaginal excision biopsy	B cell lymphoma, favor small lymphocytic lymphoma	Brachytherapy	CR	Alive, NED	20.5
50	V	mass lesion	partial colpectomy	DLBCL	Observation	CR	Alive, NED	0.22
53	V	mass lesion	vaginal biopsy	Sclerosing lymphoproliferative process	NA	NA	NA	NA
46	C	mass lesion, abnormal bleeding 2 years post hysterectomy	Trachelectomy	DLBCL	NA	CR	Alive, NED	7.8
40	V	routine screening	anterior vaginal wall excision	DLBCL	R-CHOP X 4, RCOP x 1 & involved field RT	CR	Alive, NED	16.5
37	C	abnormal bleeding	conization	FL grade 3 with areas of DLBCL	Hysterectomy, CHOP x 5 & R x 18	CR	Alive, NED	13
41	C	mass lesion	cervical biopsy and curettings	B cell lymphoma, NOS	Hysterectomy, RCVP, R-CHOP	CR/RI	Alive, NED	9.6

**60% diagnosed as DLBCL**

**median follow-up 7.8 years**

Saksena A. et al, AJSP, 2023