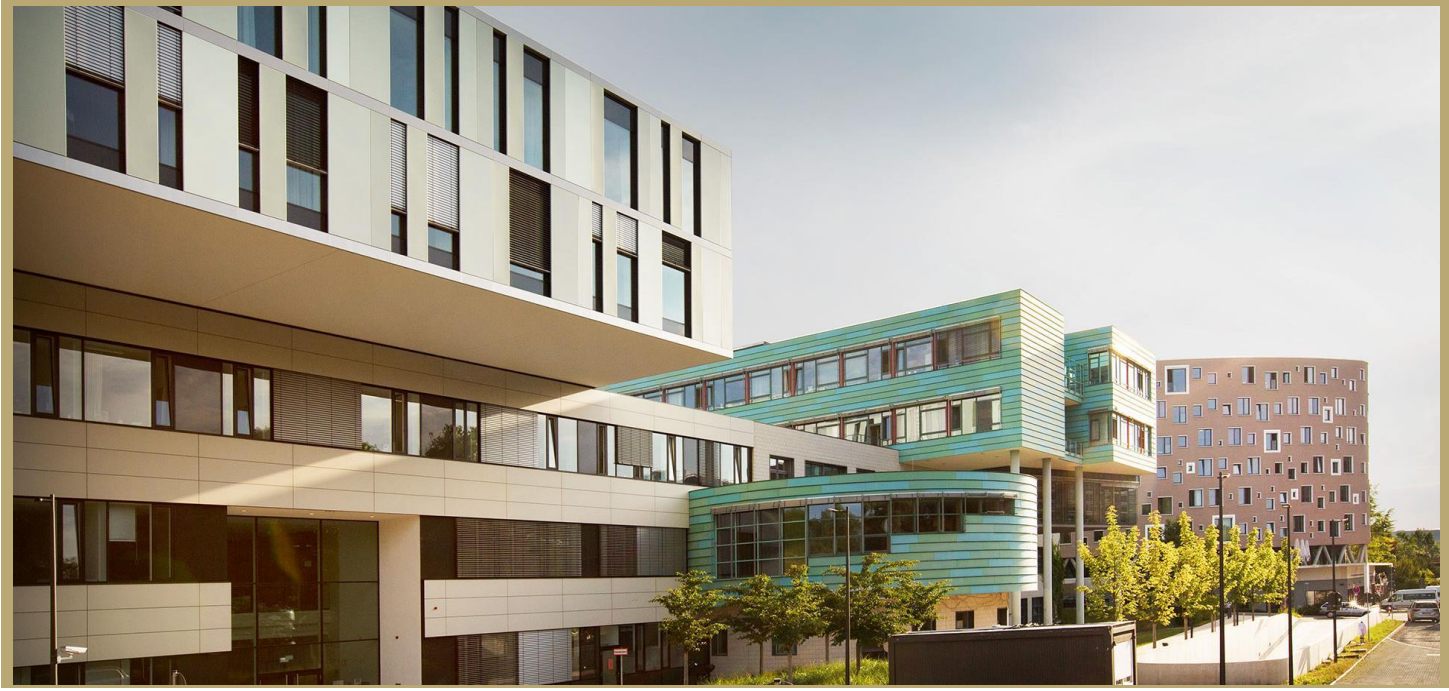
Reactive Lymphadenopaties in children and young adults and ist differential diagnosis with malignant proliferations



LYMPHOMA Forum of Ireland

20th lymphoma Forum of Ireland Plenary meeting

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Reactive lymphadenitis and mimics

- Objectives:
- To review the most common lymphadenitis in children and young adults
- To review some differential diagnosis between reactive and malignant proliferations.

LYMPHOMA
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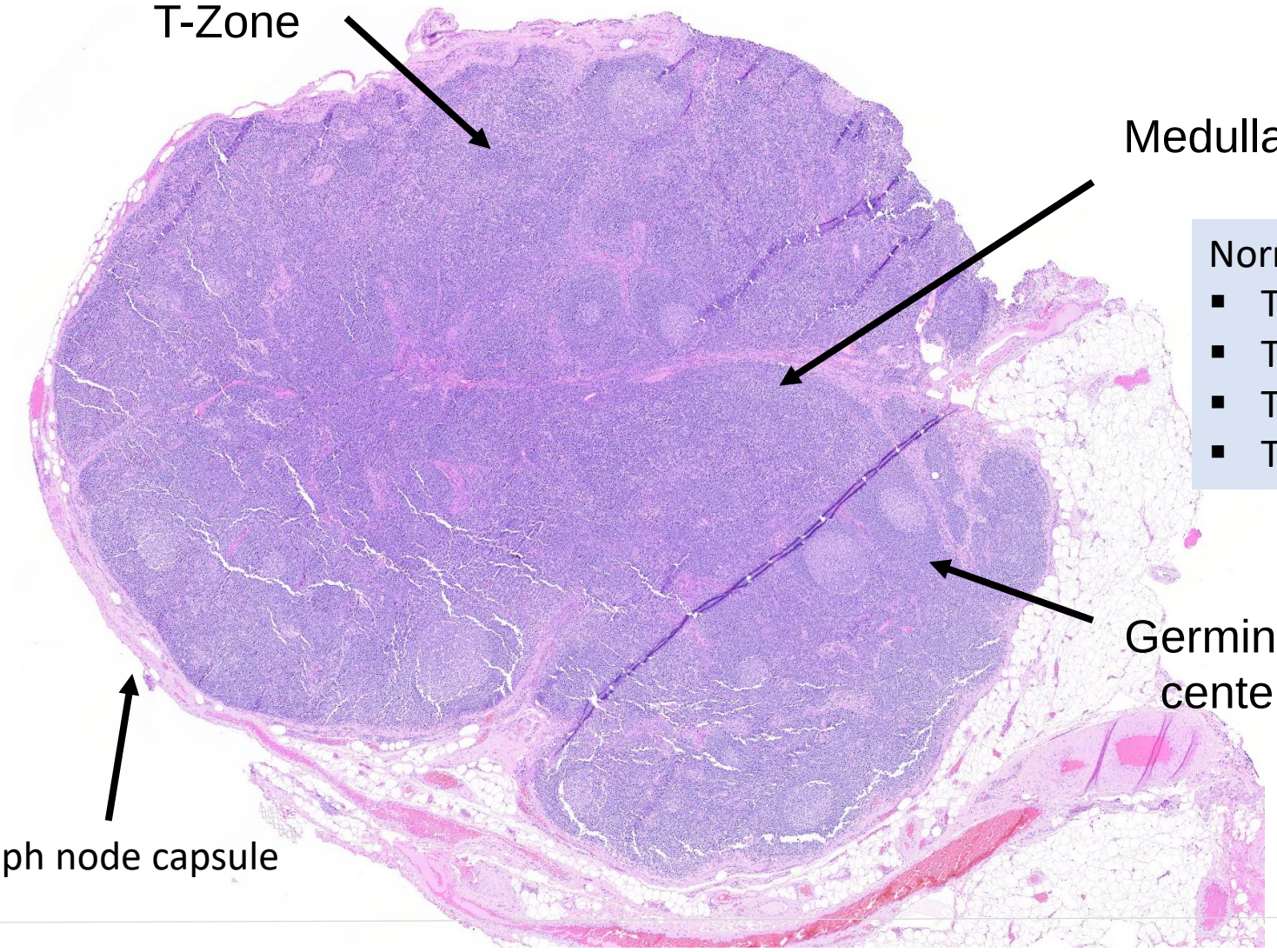
Reactive lymphadenitis and mimics



Normal lymph node architecture

- The capsule is preserved
- The germinal centers are subcapsular
- The interfollicular zone (T-zone) is not expanded
- The sinuses are often (medulla)

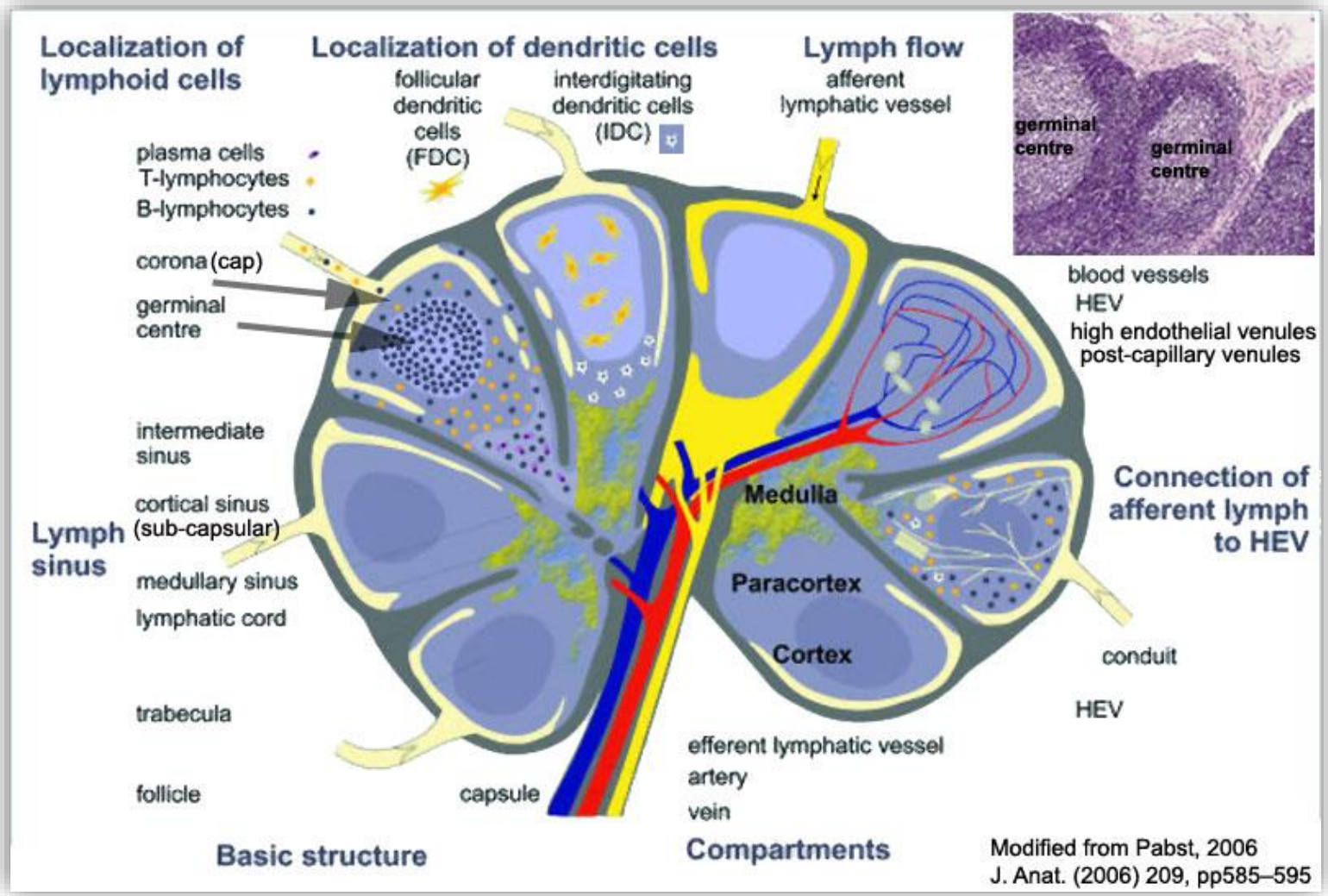
Reasons for altered lymph node architecture

- Is there a „normal“ lymph node architecture?
- Functional states defines the morphology
  - Lack of stimulation – inactive o regressive
  - Immunological activation
    - B-cell activation – follicular hyperplasia
    - T-cell stimulation: T-zone hyperplasia
    - Other: marginal zone/monocytoid B-cell hyperplasia, plasmacytosis and sinus hyperplasia
- In immunological activation, the basic structure of the lymph node is usually preserved.

- Disruption of the architecture by a reactive process
  - Infectious
  - Non-infectious
- Disruption by infiltration of malignant process
  - Hematolymphoid
  - other

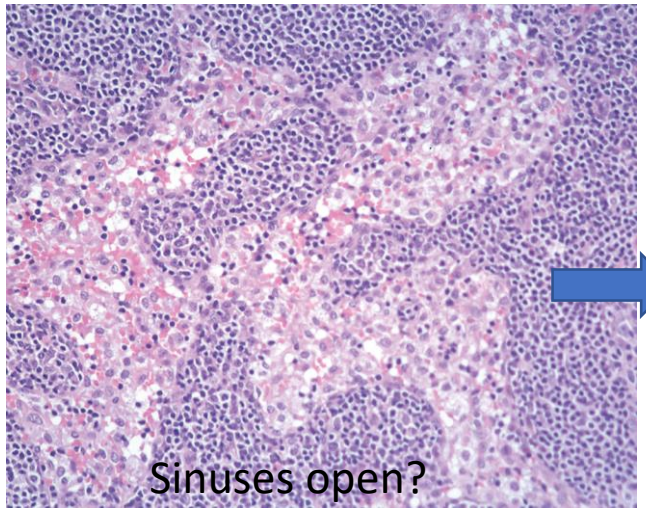
Reactive lymphadenitis and mimics

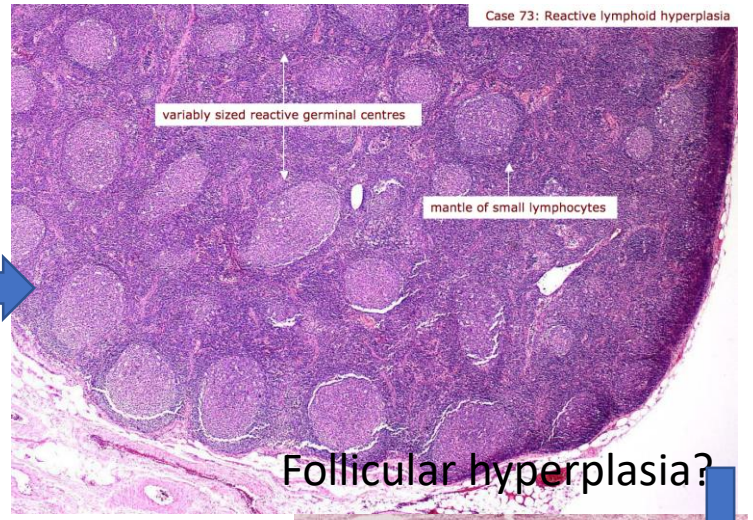
- Follicular and nodular patterns
  - Follicular hyperplasia
  - Autoimmune disorders
  - Systemic Lupus erythematosous
  - Progressive transformation of germinal centers
  - Castleman disease, hyaline vascular type
- Predominantly sinus pattern
  - Sinus histocytosis
  - Hemophagocytic lymphohistiocytosis
- Interfollicular or mixed patterns
  - Dermatopathic lymphadenopathy
  - Granulomatous lymphadenitis
    - Toxomplasma lymphadenitis
    - Kikuchi lymphadenitis
- Diffuse Pattern
  - Infectious mononucleosis
  - Cytomegalovirus infection
  - Herpes simplex lymphadenitis

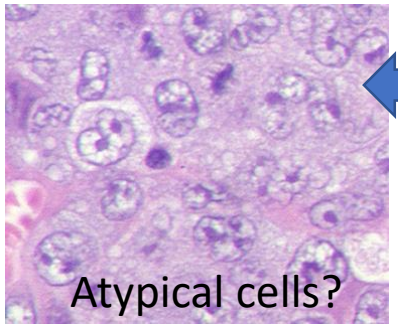


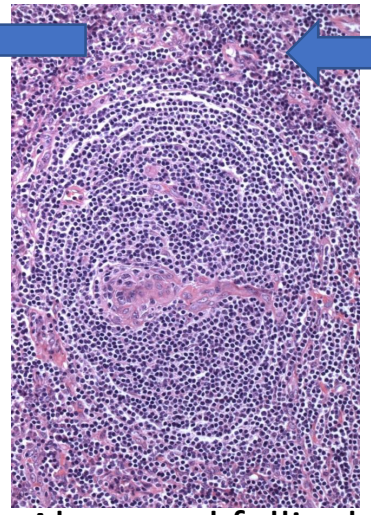
Morphological check-list

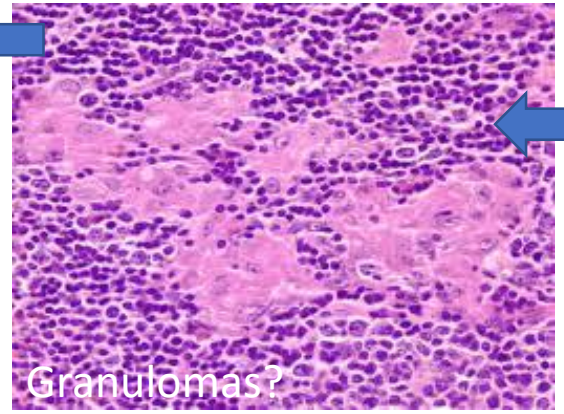
- Capsule preserved/extracapsular infiltrate?
- Sinuses open?
- Architecture preserved? Completely/partially?
  - Follicles/germinal centers
    - Primary/secondary follicles present?
    - Correctly located?
    - Starry sky pattern?
    - polarization?
  - T-zone
    - preserved?
    - Activated?
  - Special reaction patterns?
    - Granulomas
    - Monocytoid B-cell reaction
    - Plasmacytosis, interfolicular blasts….
  - Atypical cell populations identifiable?

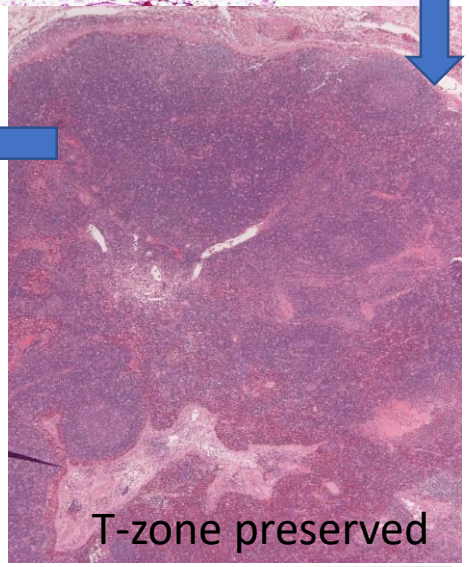




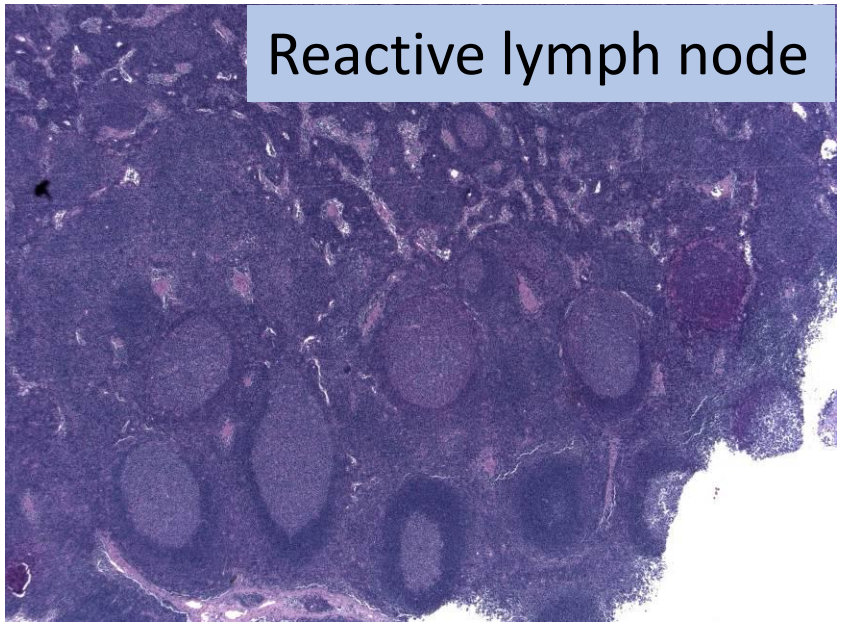


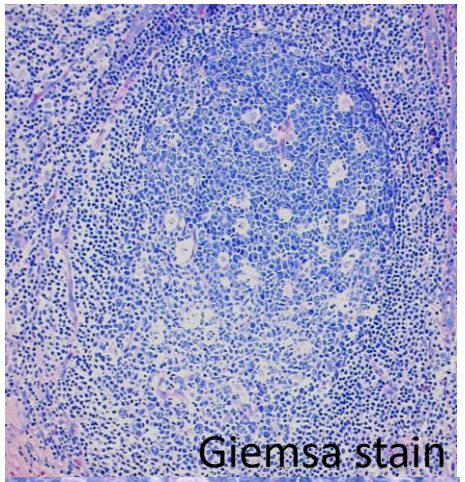


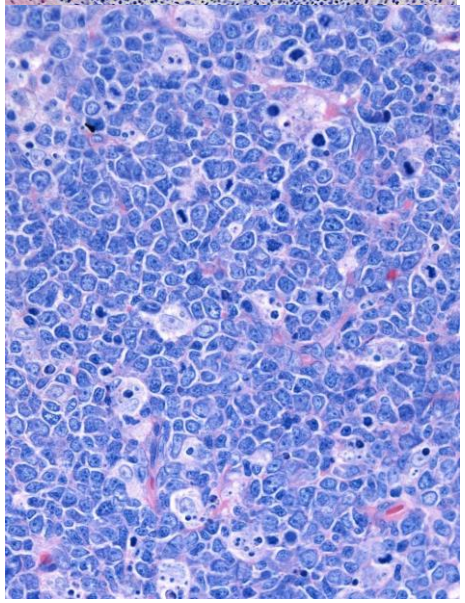


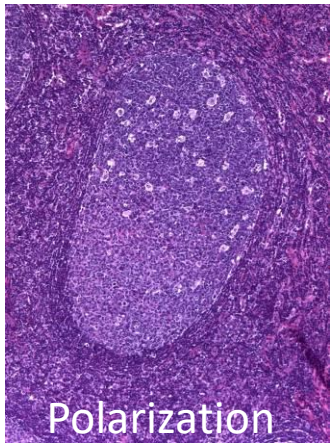


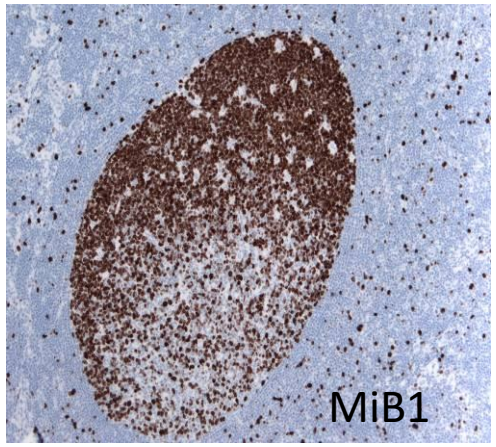
B-cell follicles

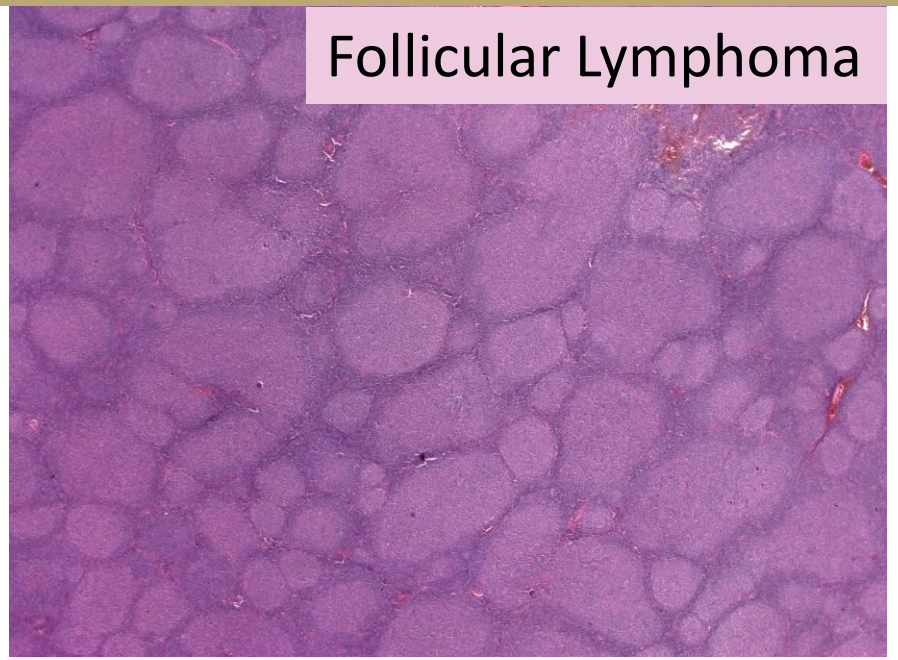


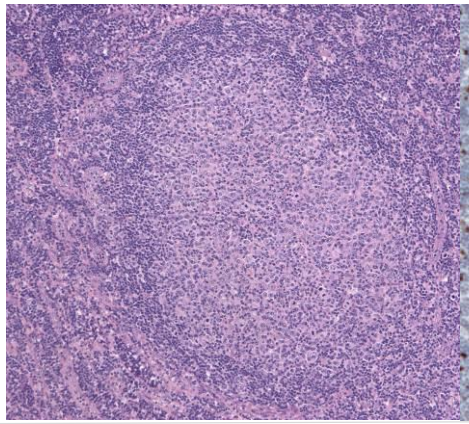


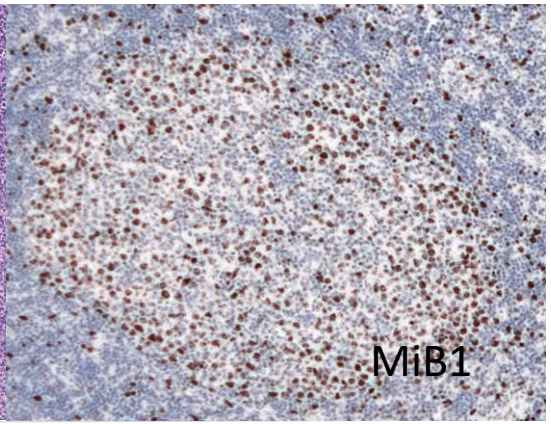






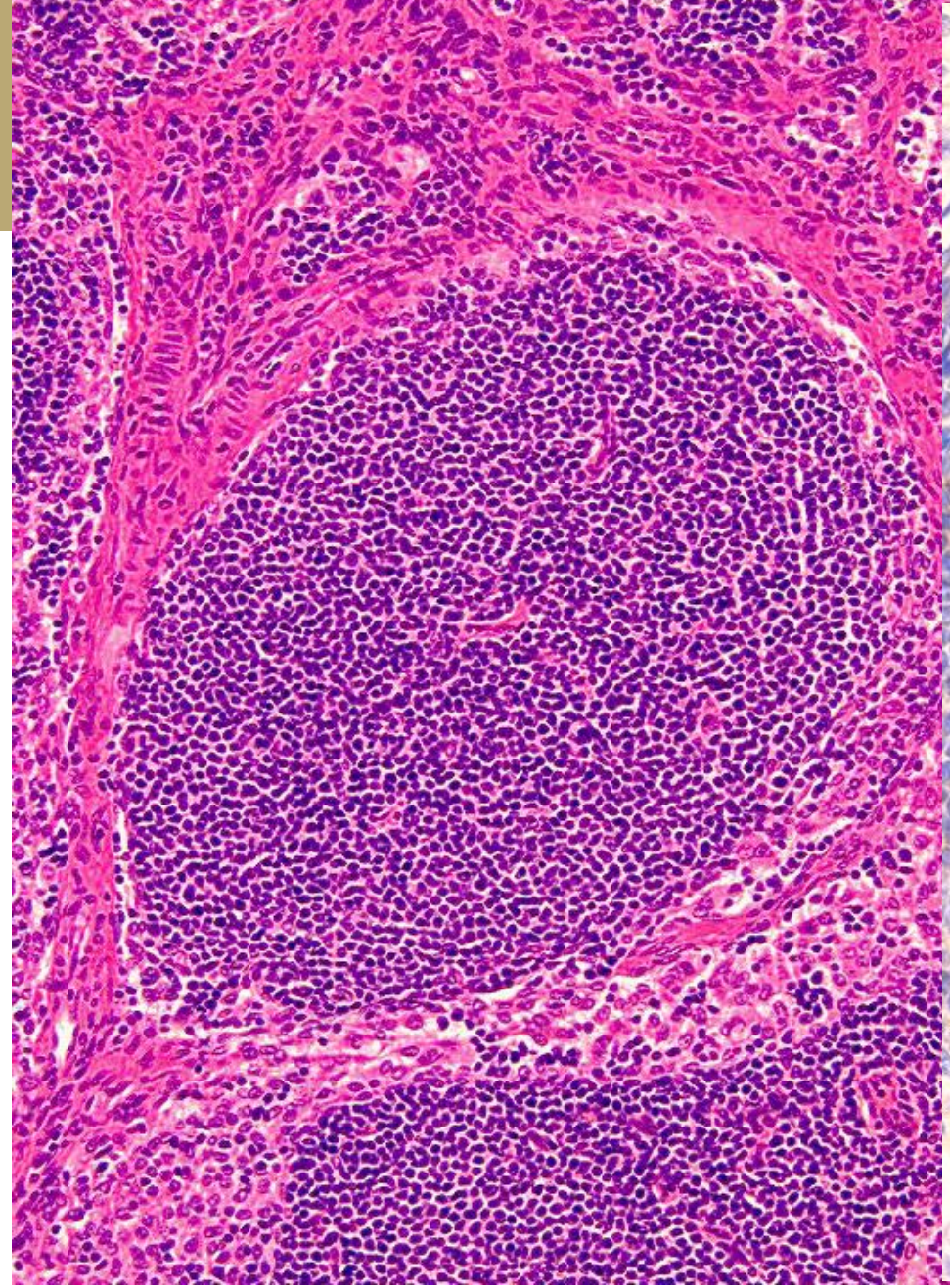


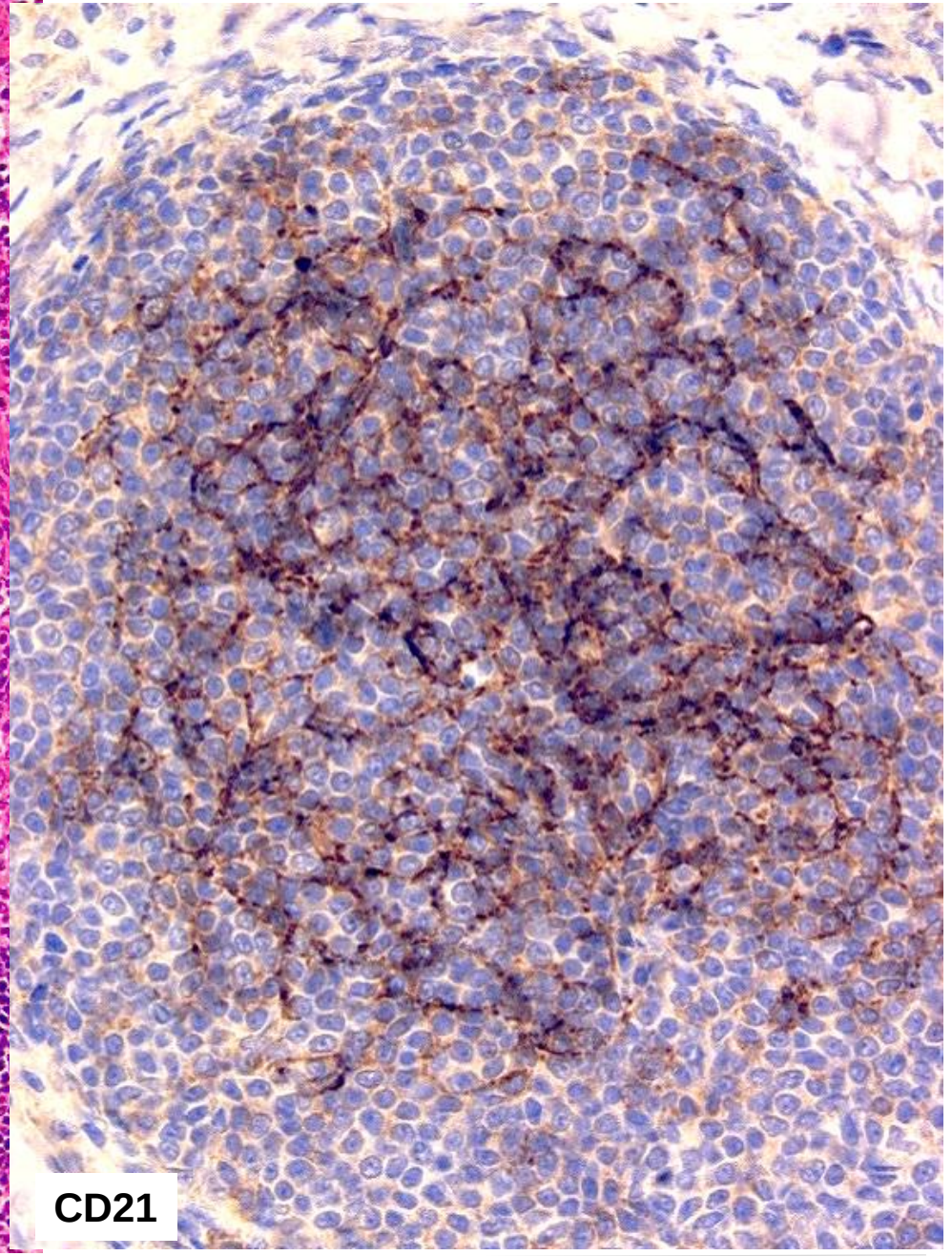




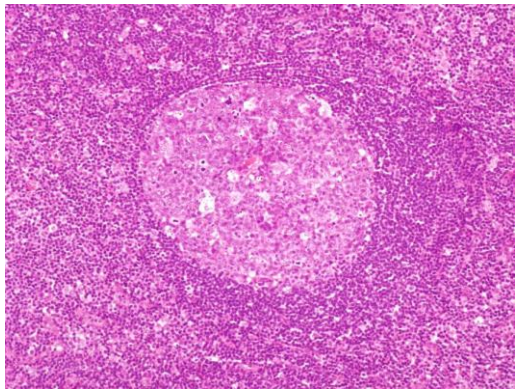
Primary follicles

- The cells look monotonous
- Low proliferatio rate
- BCL2+
- IGD+
- CD10-
- BCL6-
- Presence of FDC´s

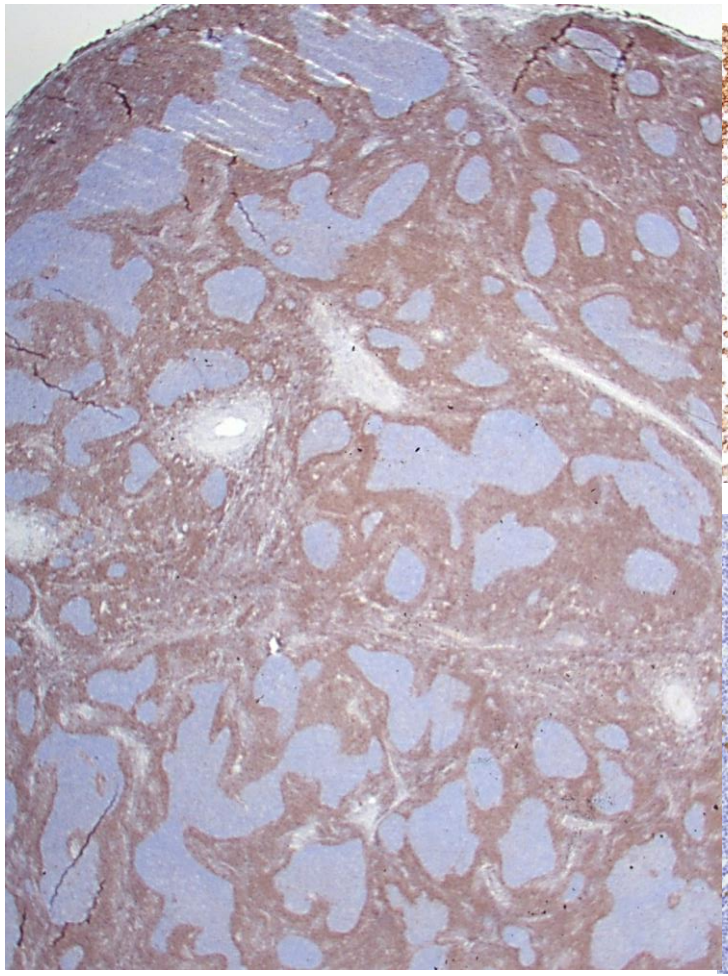


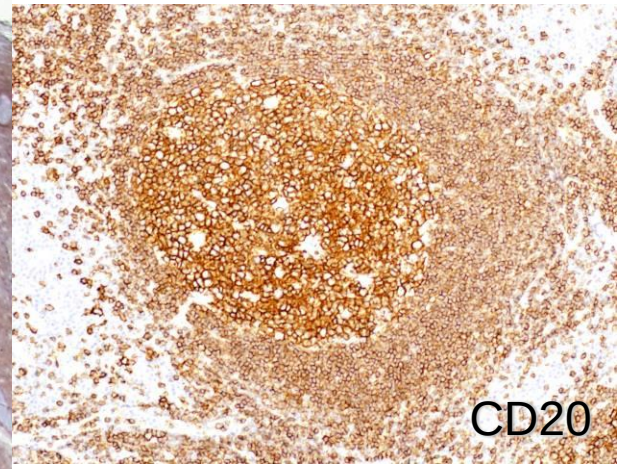


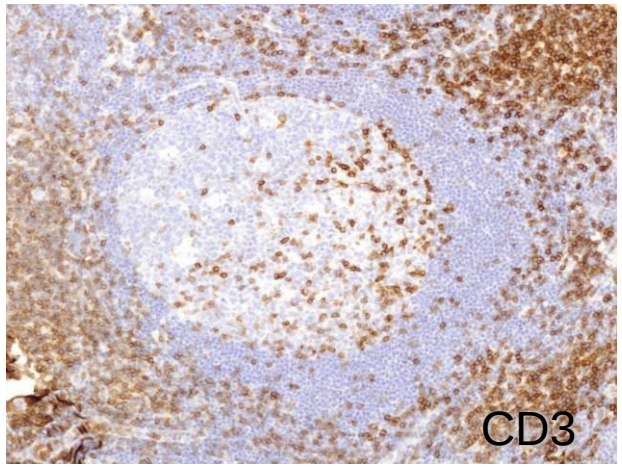
Reactive follicular hyperplasia

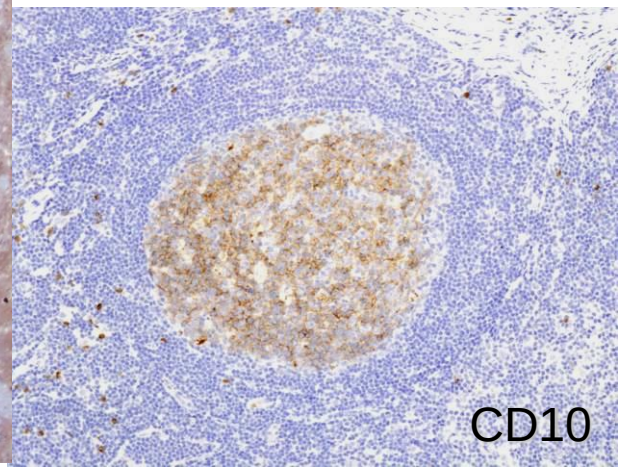


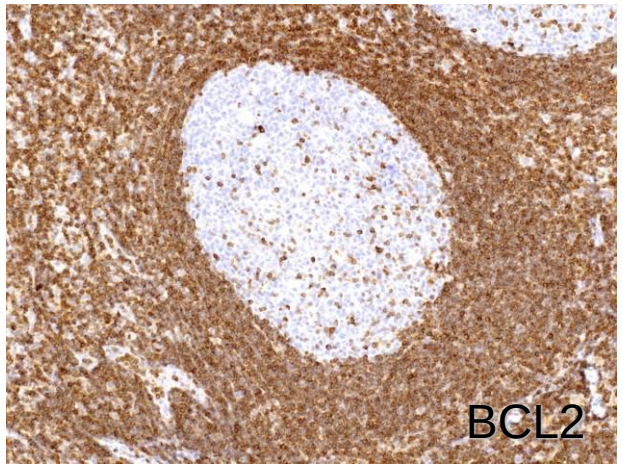
- variable size and shape
- numerous mitoses
- polarization of GC
- numerous centroblasts
- starry sky appearance of GC (tingible body macrophages)
- GC B-cells are BCL2 negative and polytypic





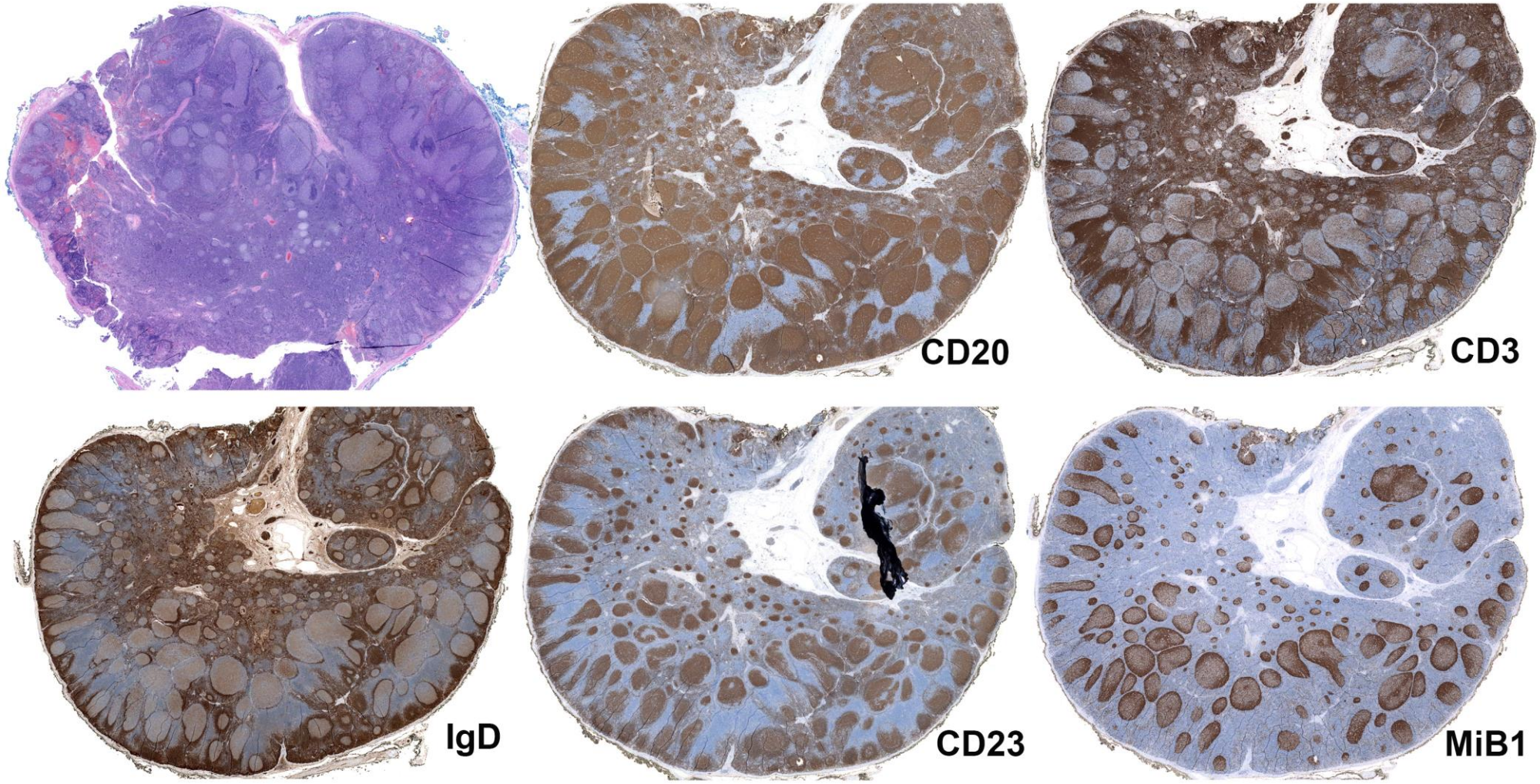






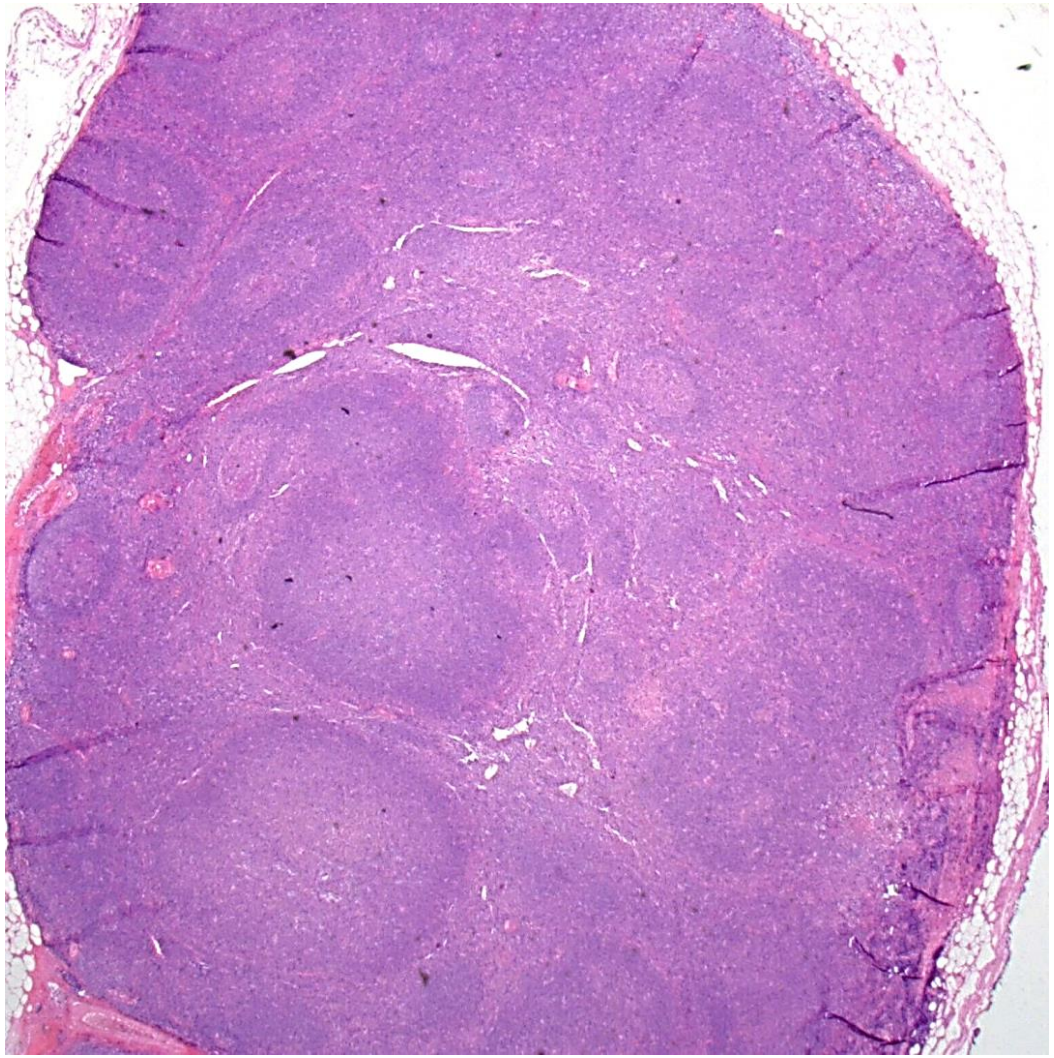
Follicular hyperplasia, non-specific

- 7-year-old boy with a large cervical lymph node
- The patient is known because of Burkitt lymphoma diagnosed in 2022

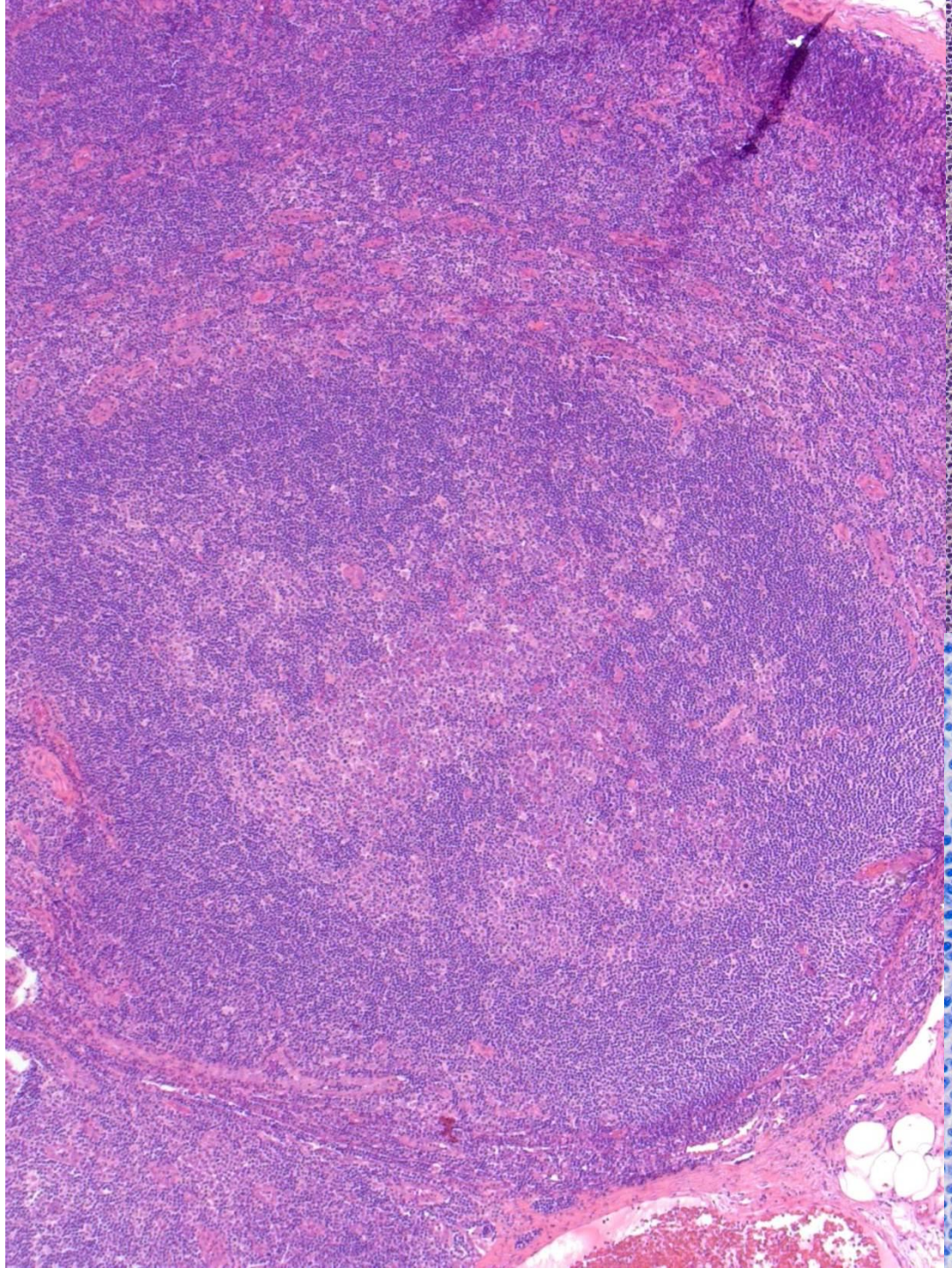


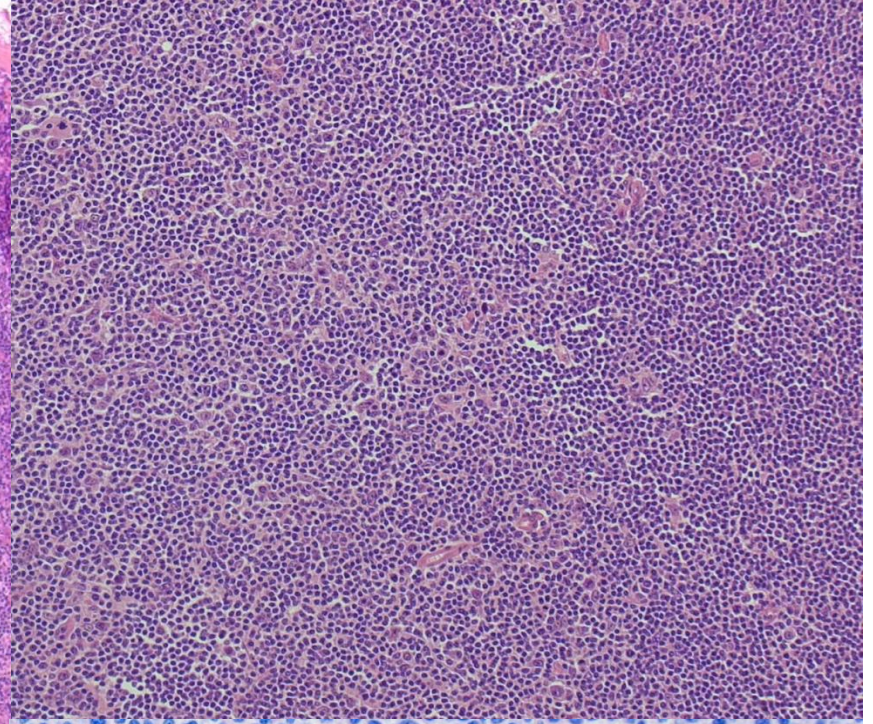
Progressive transformation of germinal centers (PTGC)

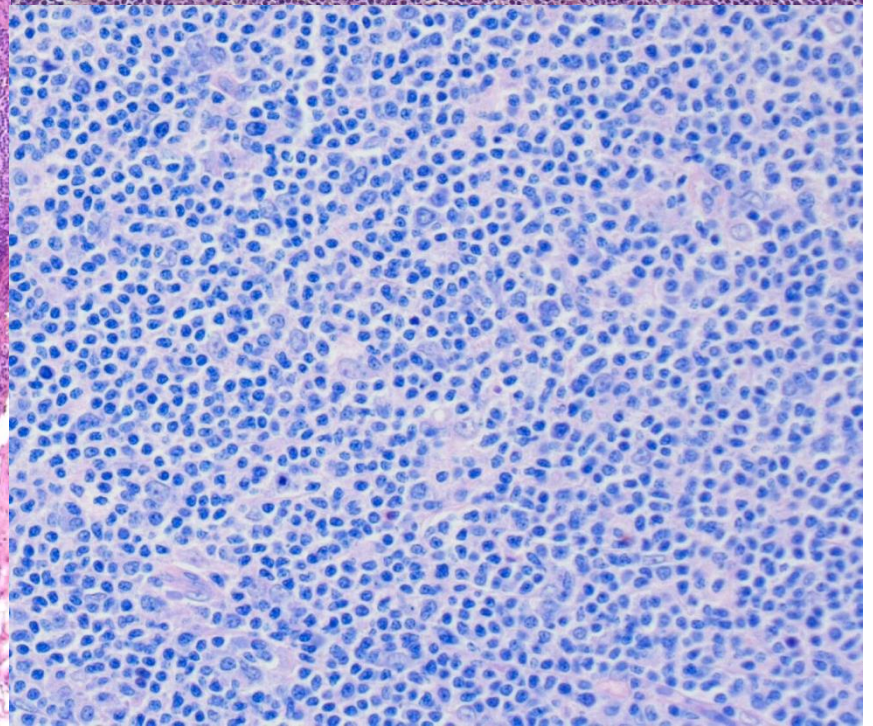
12-year-old boy with cervical lymphadenopathy

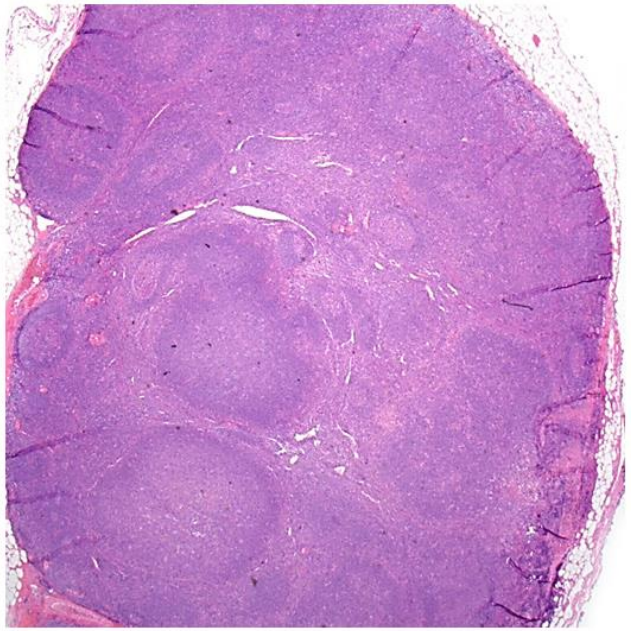


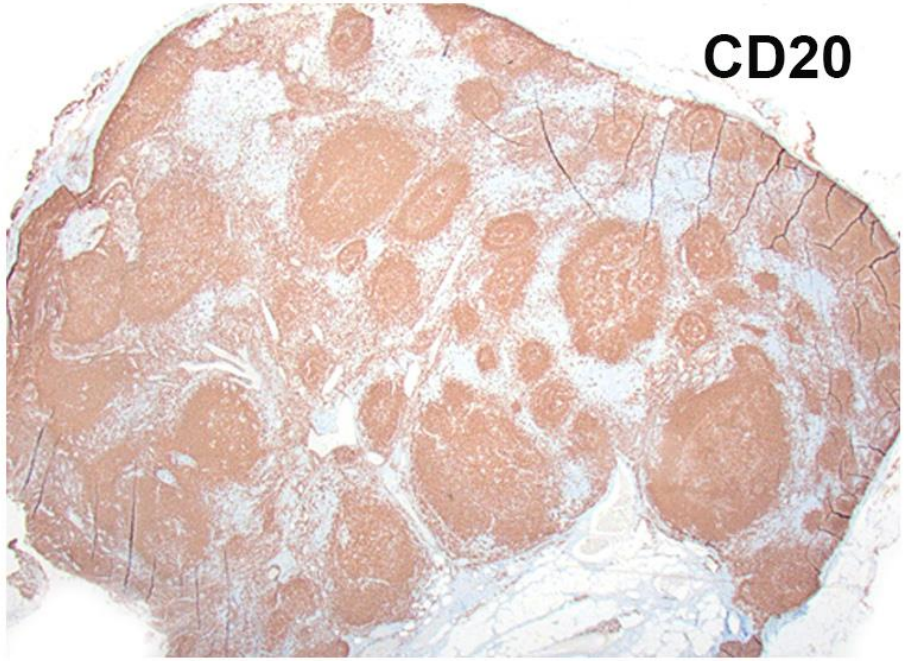
- Reactive change of B-cell follicles
- Usually admixed with normal germinal centres
- Enlarged B-cell nodules with destruction of GC and invasion of mantle cells
- IgD+ lymphocytes, expanded CD23+ FDC meshworks, residual BCL6/CD10+ GC cells
- Many PD1/CD57+ TFH cells

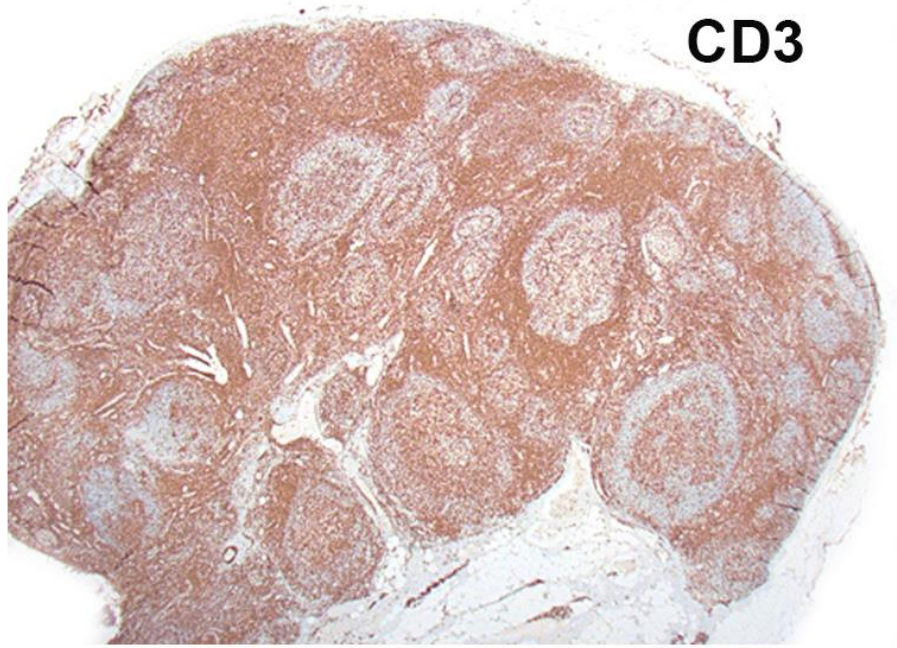


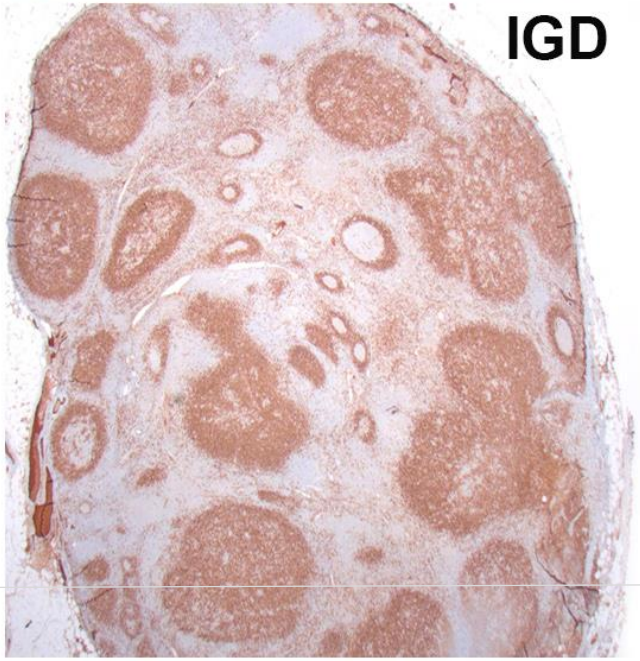


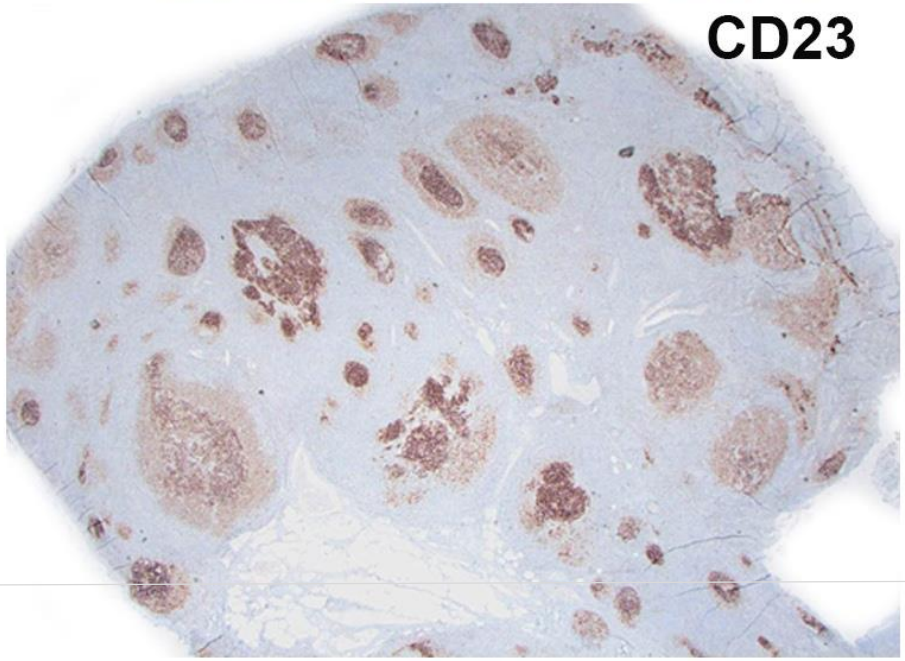


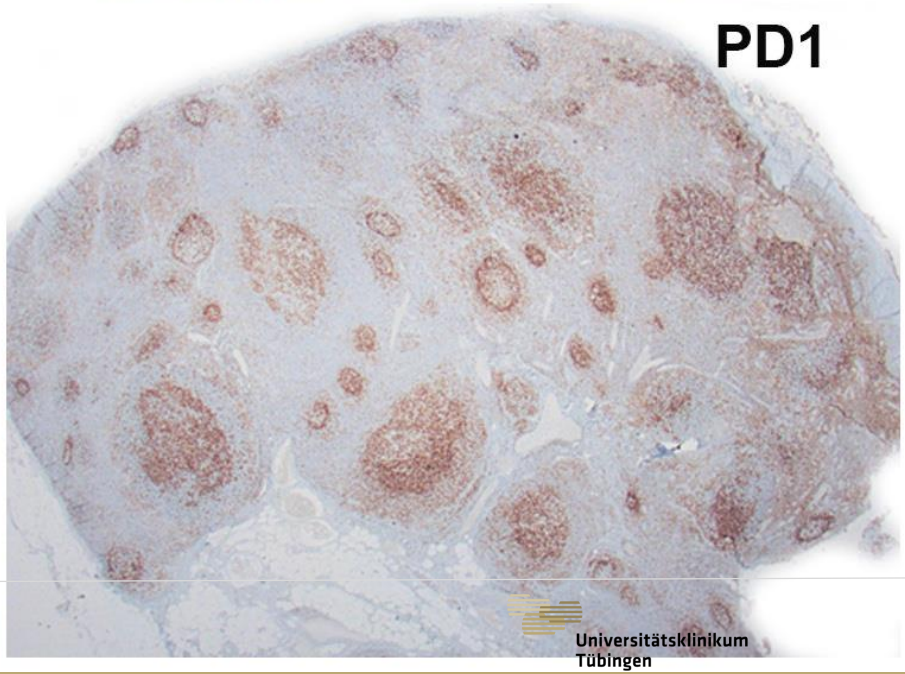



CD20


CD3

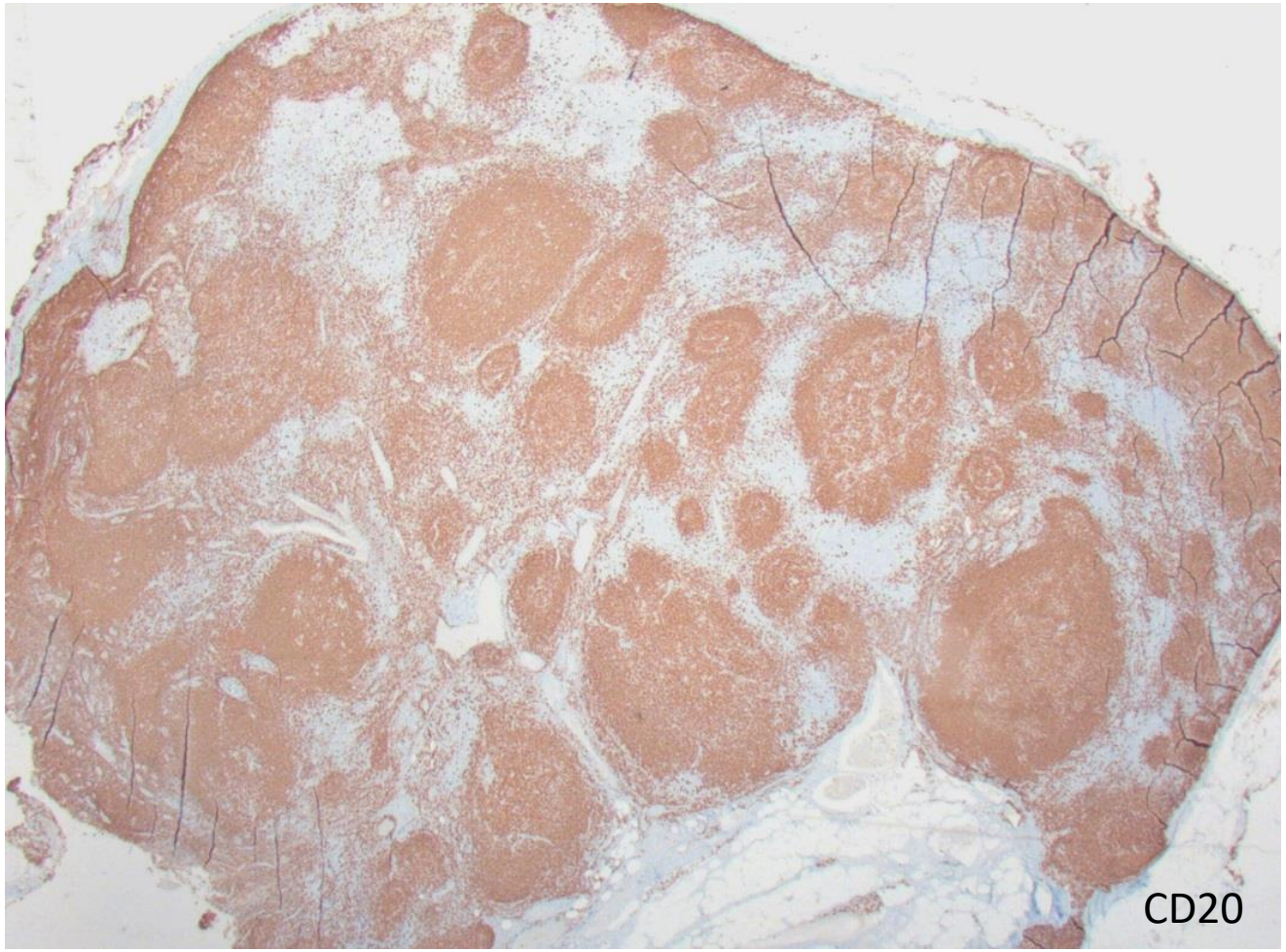

IGD


CD23


PD1

Progressive transformation of germinal centers (PTGC)

- PTGC is a pattern of reactive lymphadenopathy
- Usually single enlarged LN in asymptomatic individulas
- Affects children and young adults
- Cervical and axillary LN most commonly involved
- PTGC can also be seen in autoimmune phenomena in pediatric population
- Can precede or follow CHL



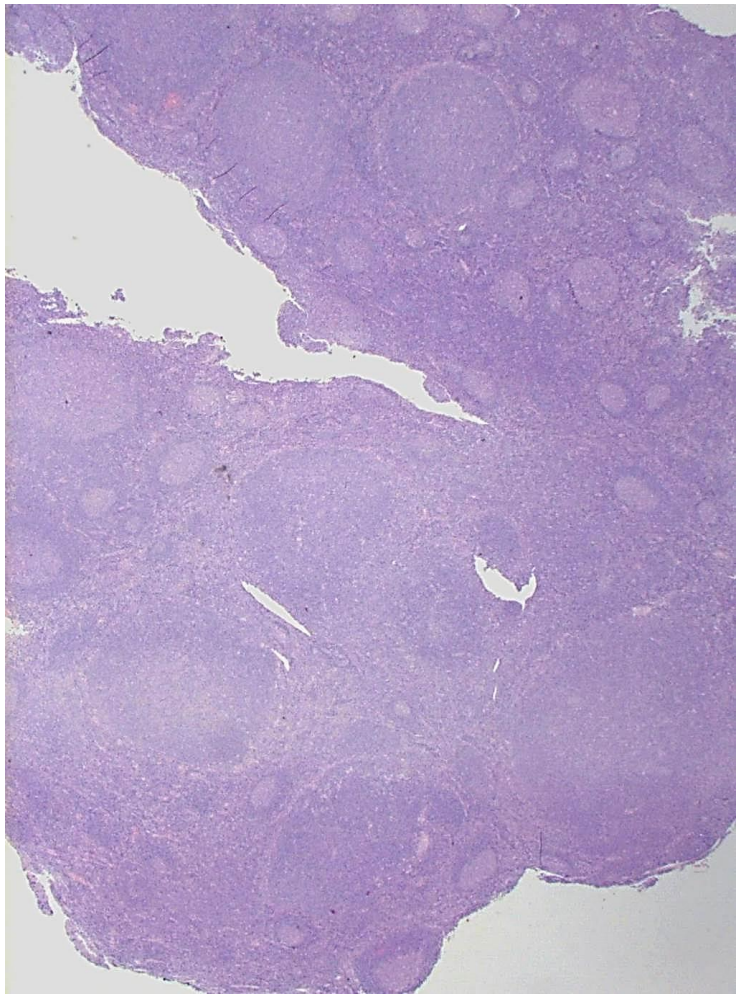
Beware of mimics

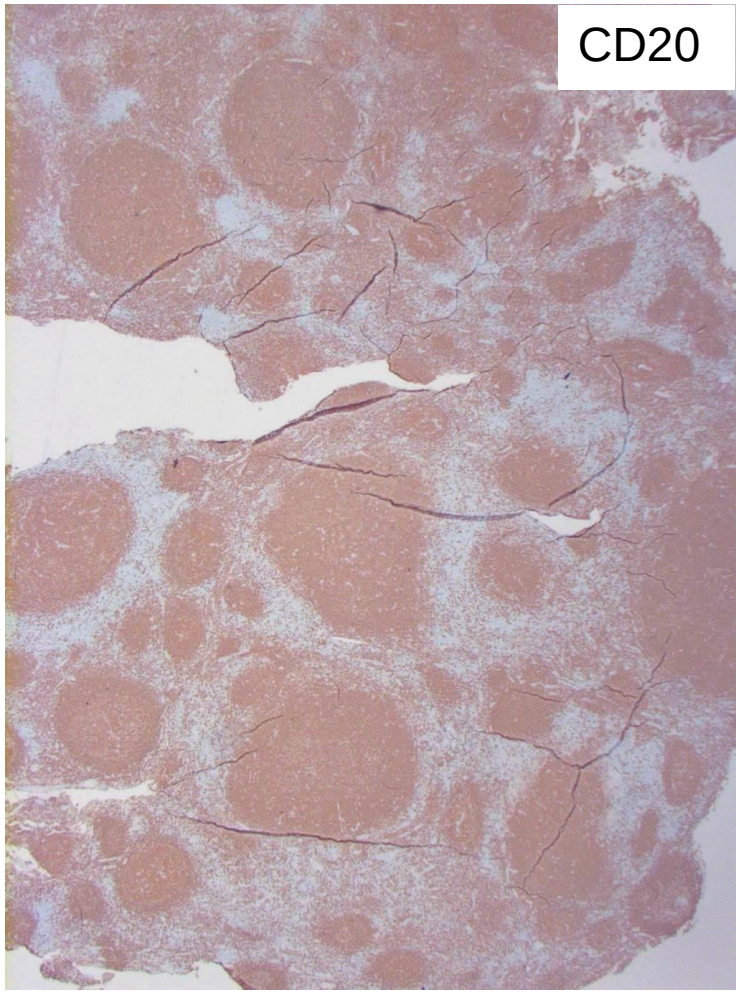
PTGC-like pattern

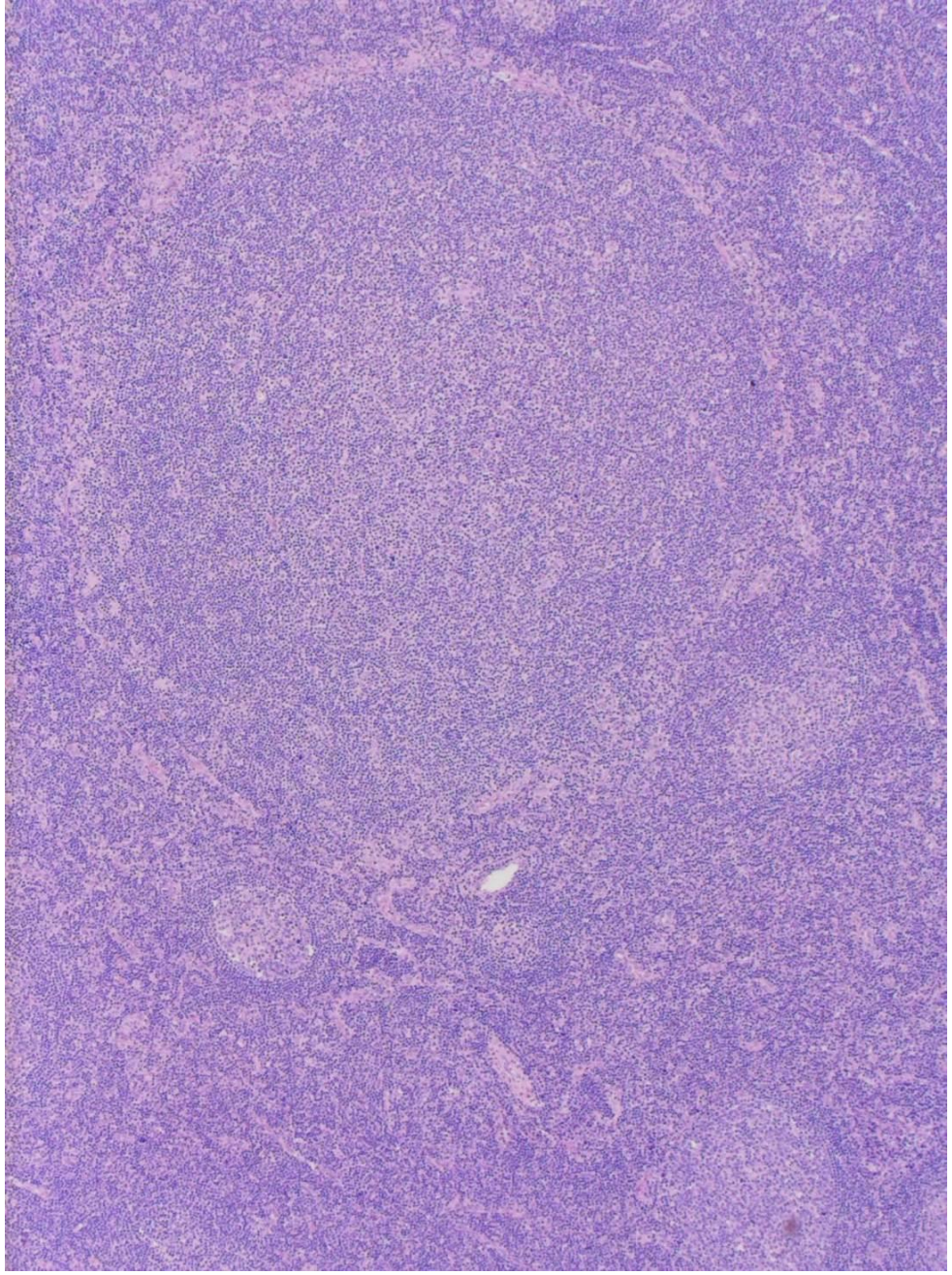
- Nodular lymphocyte predominant B-cell lymphoma (NLP)
- Pediatric-type follicular lymphoma
- *Pediatric nodal marginal zone lymphoma*
- IGG4-related lymphadenopathy
- others

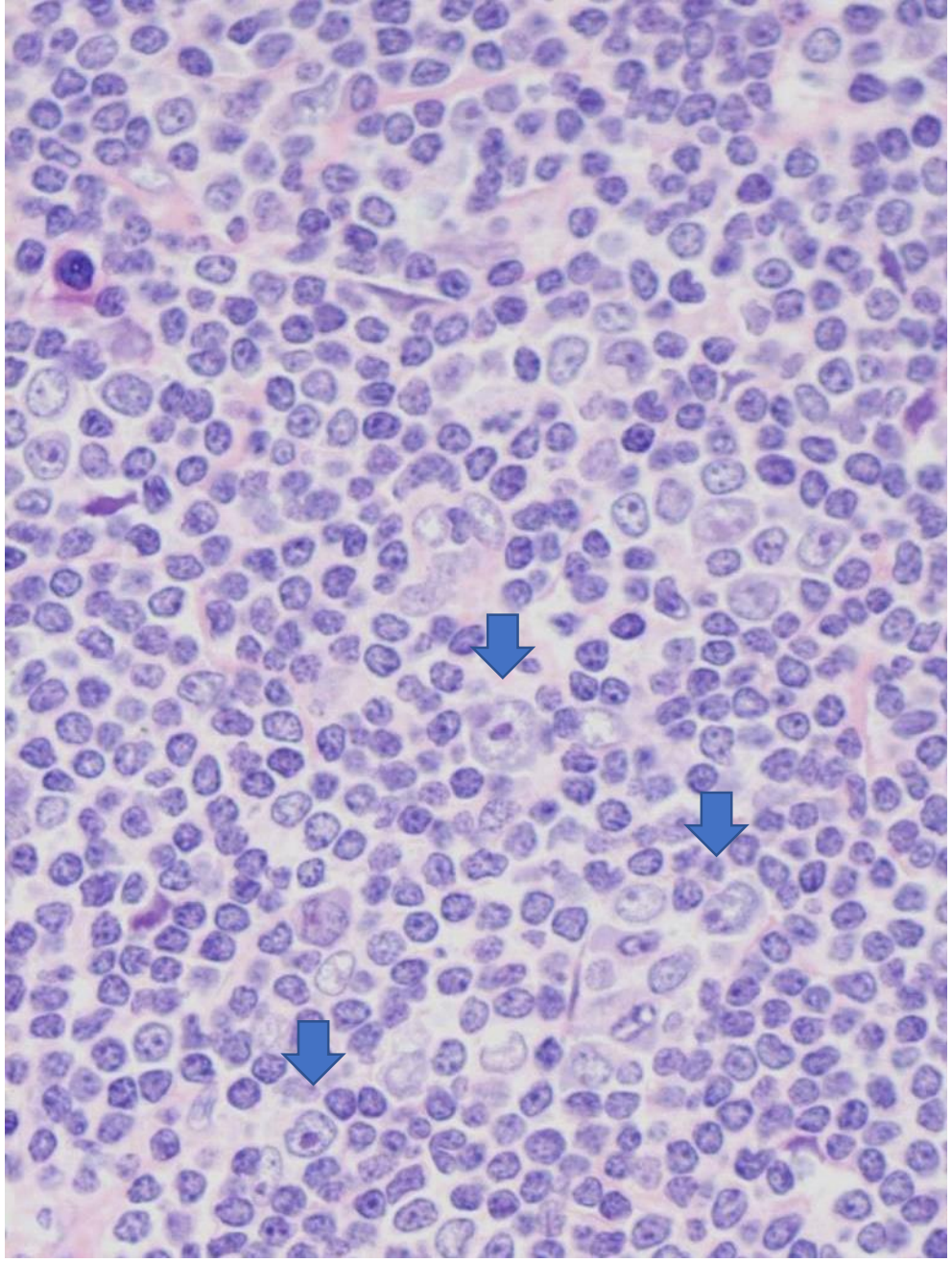
Progressive transformation of germinal centers?

- A 23 year old male, axillary LN, history of lymphoma, 5 years ago

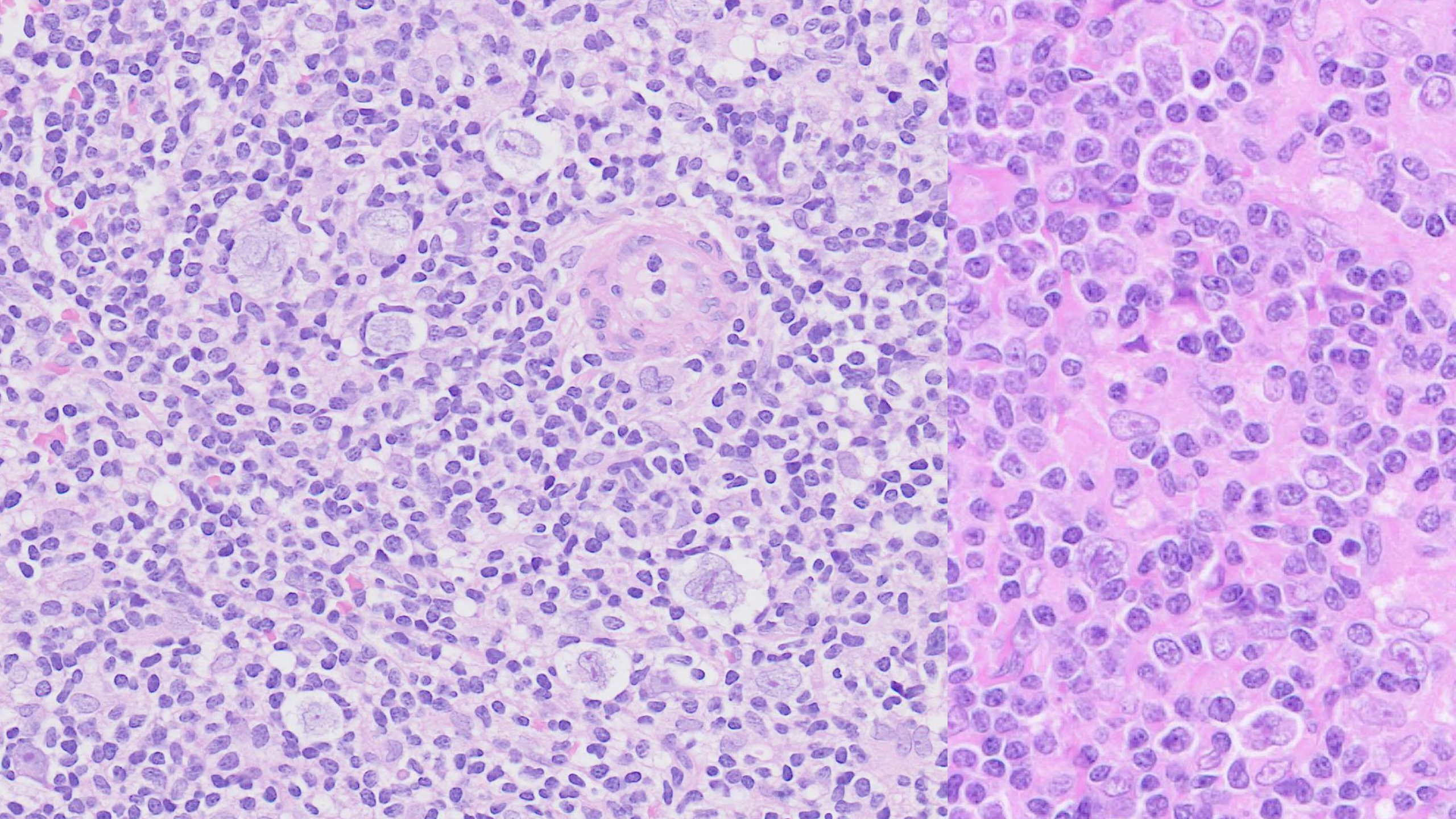








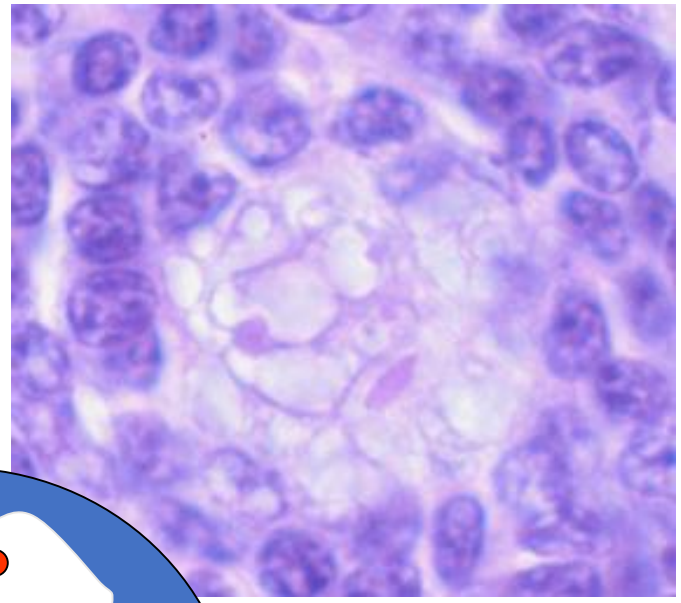
Large cells with open chromatin and usually one or more large eosinophilic nuclei known as „LP“ cells



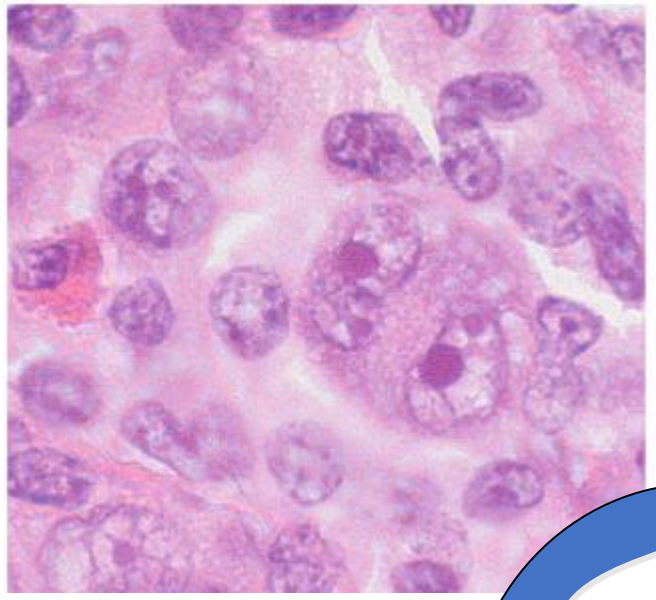
Nodular lymphocyte predominant B-cell lymphoma

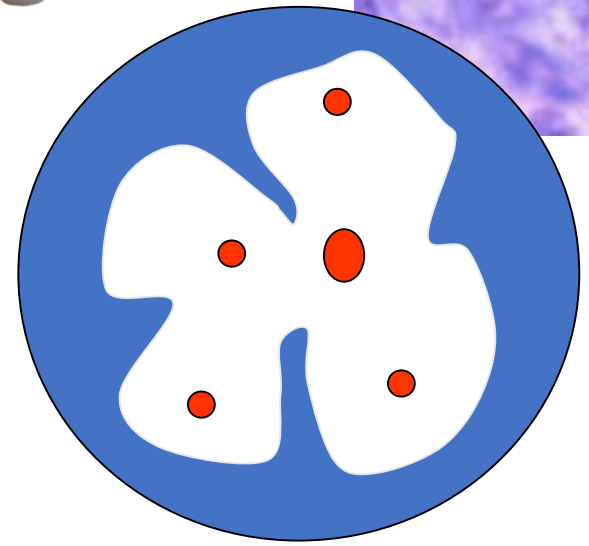
„pop-corn cell“

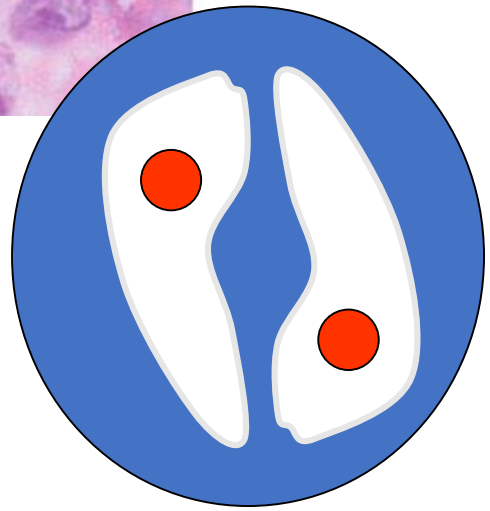
NLPBL



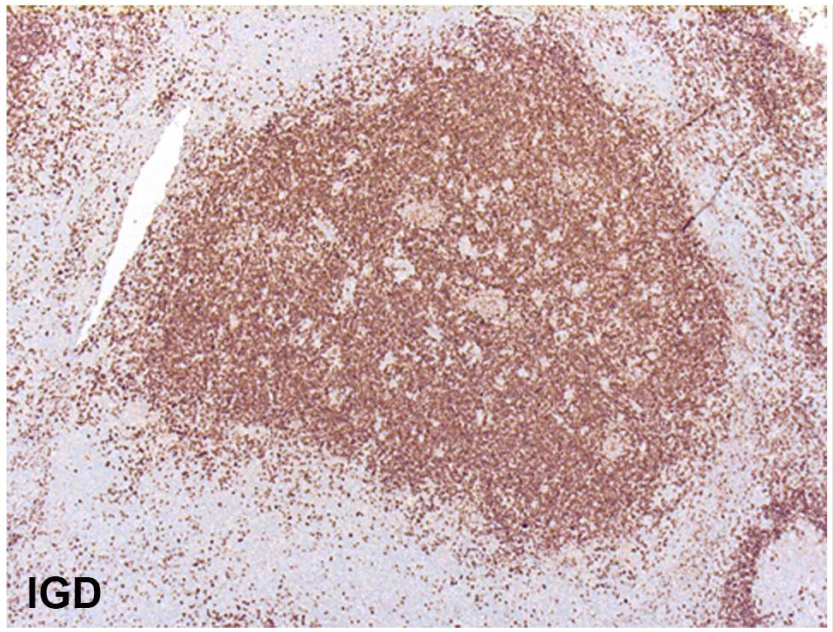
CHL



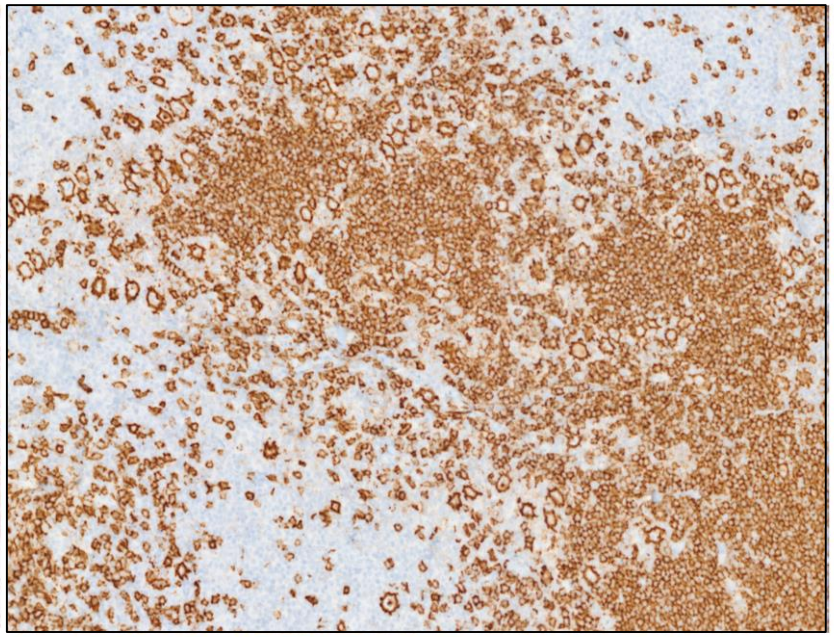




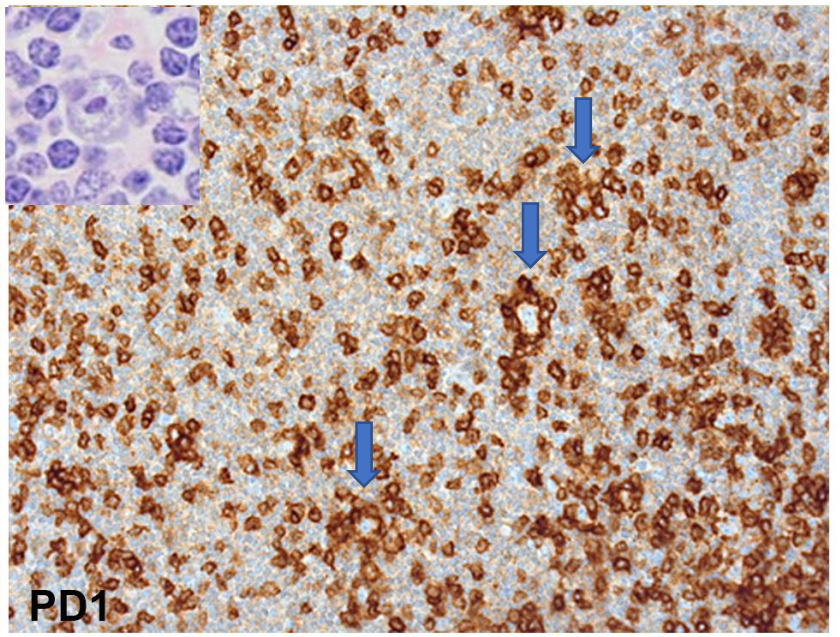
Nodular lymphocyte predominant B-cell lymphoma



PTGC pattern

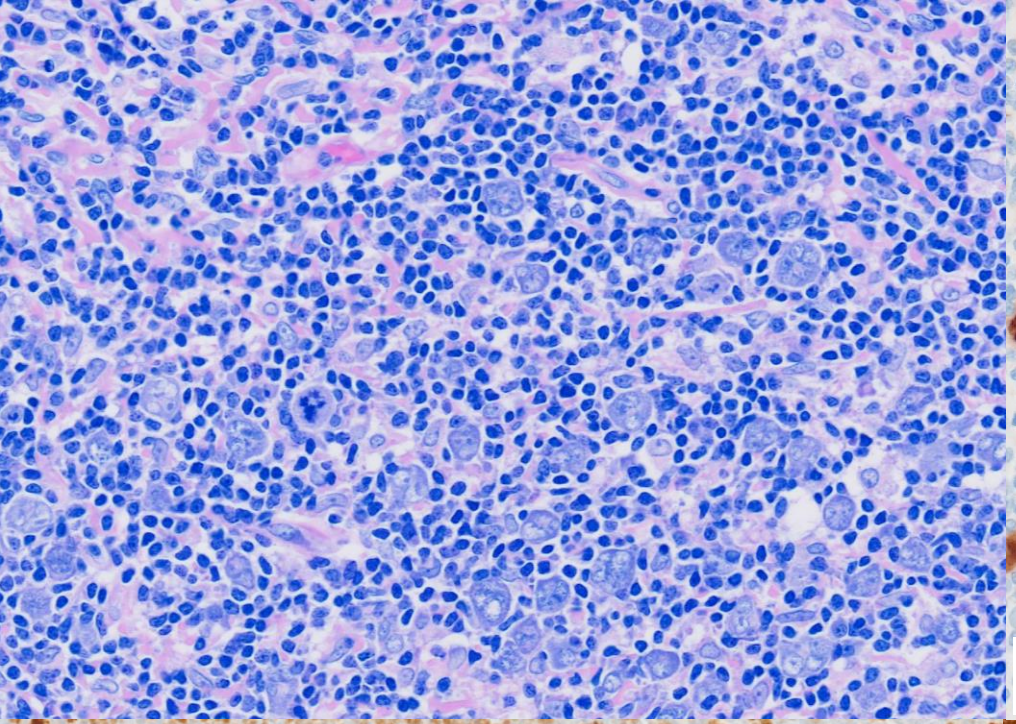


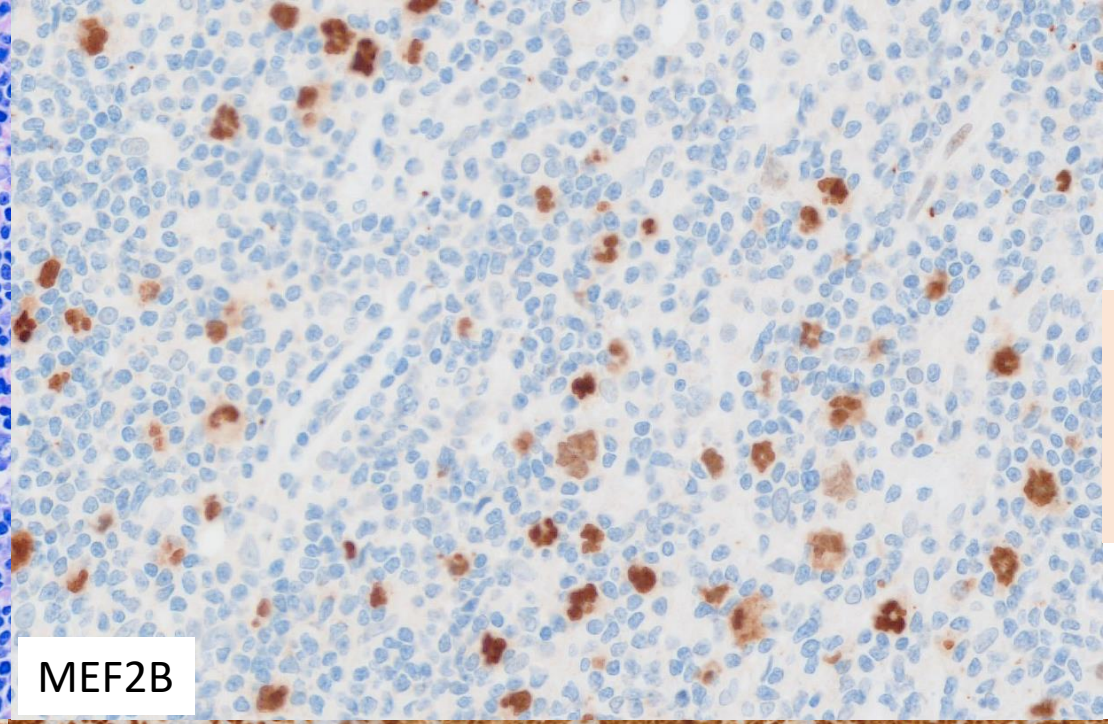
Large atypical CD20+ B-cells



PD1+ rosettes

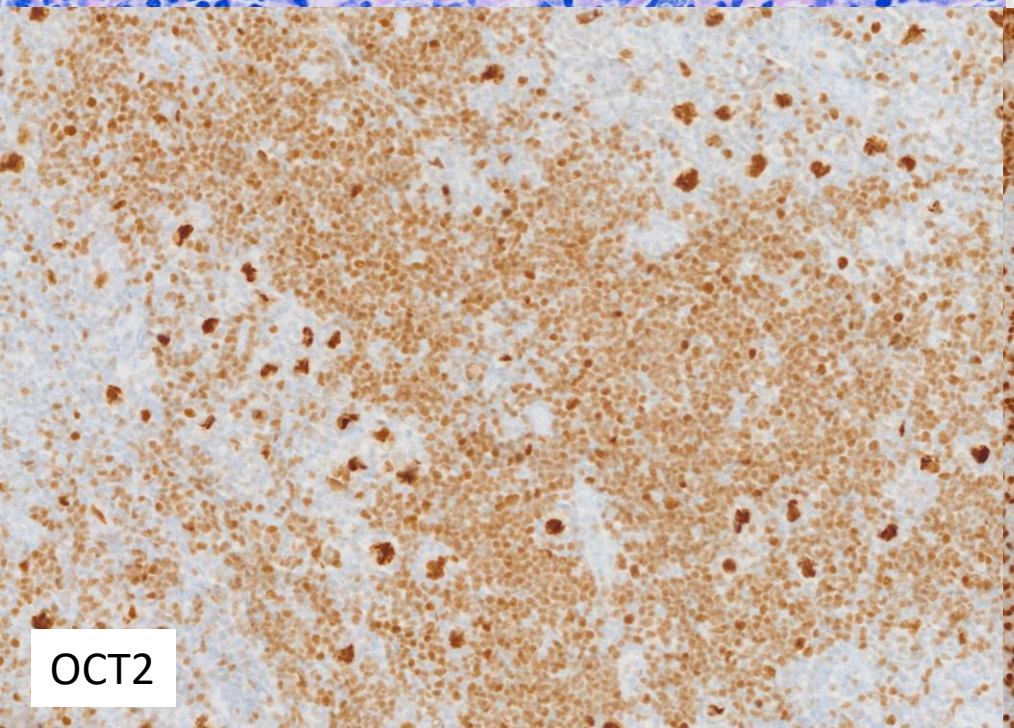
Diagnosis:
Nodular lymphocyte predominant B-cell lympoma (nodular paragranuloma or NLPHL) recurrence after 5 years
DD with PTGC relies on demonstration of *bona fide* LP cells (CD20+) and PD1/CD57 rosettes – don‘t overcall!





MEF2B

GC marker reliably positive in NLPBL and negative in CHL



OCT2

PAX5

Usually strong expression of B cell TF OCT2 and BOB.1

PAX5 sometimes reduced compared to normal B cells

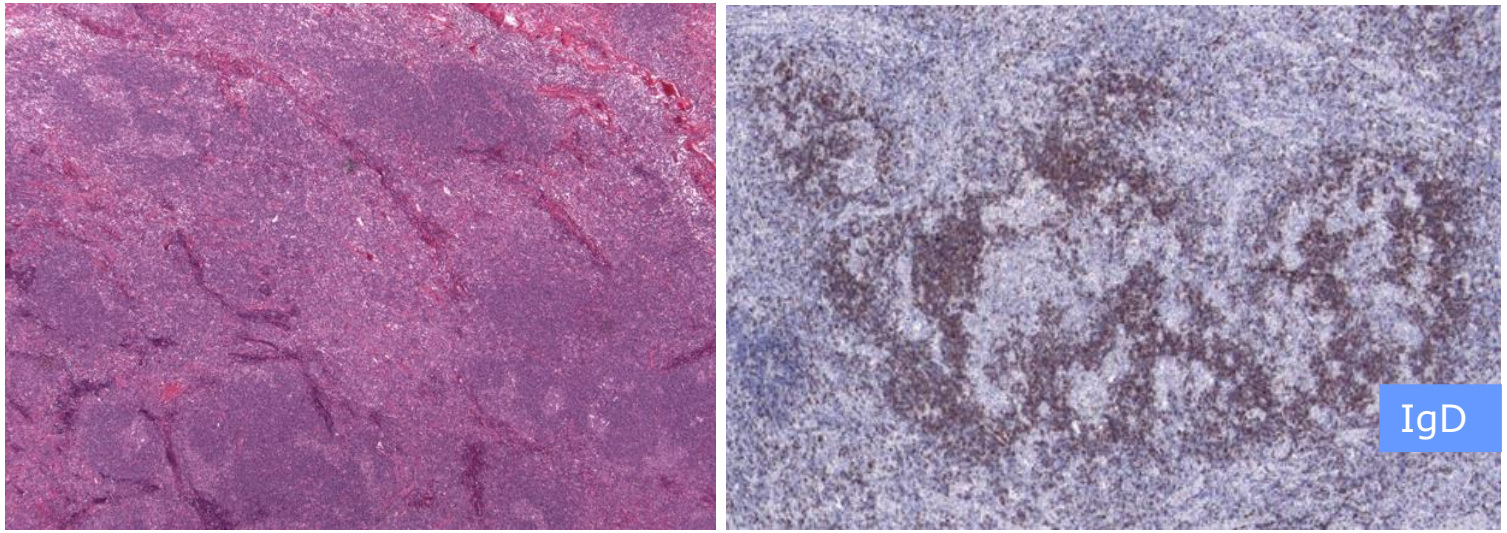
Reactive follicular hyperplasia or lymphoma?

- Pediatric nodal marginal zone lymphoma
- Pediatric-type follicular lymphoma
- Conventional follicular lymphoma

Pediatric nodal marginal zone lymphoma

- Clinically
  - Young males
  - head and neck LN
  - median age 16 years (2-27)
  - M:F ratio 20:1 (<18 years)
  - 90% stage I
  - Excellent prognosis, low rate of recurrence
- Morphologically
  - PTGC-like features
  - Expanded marginal zone (Interfollicular distribution)
- Genetically
  - Monoclonal IGH gene

PTGC like features with expanded and disrupted IgD+ mantle zone cells



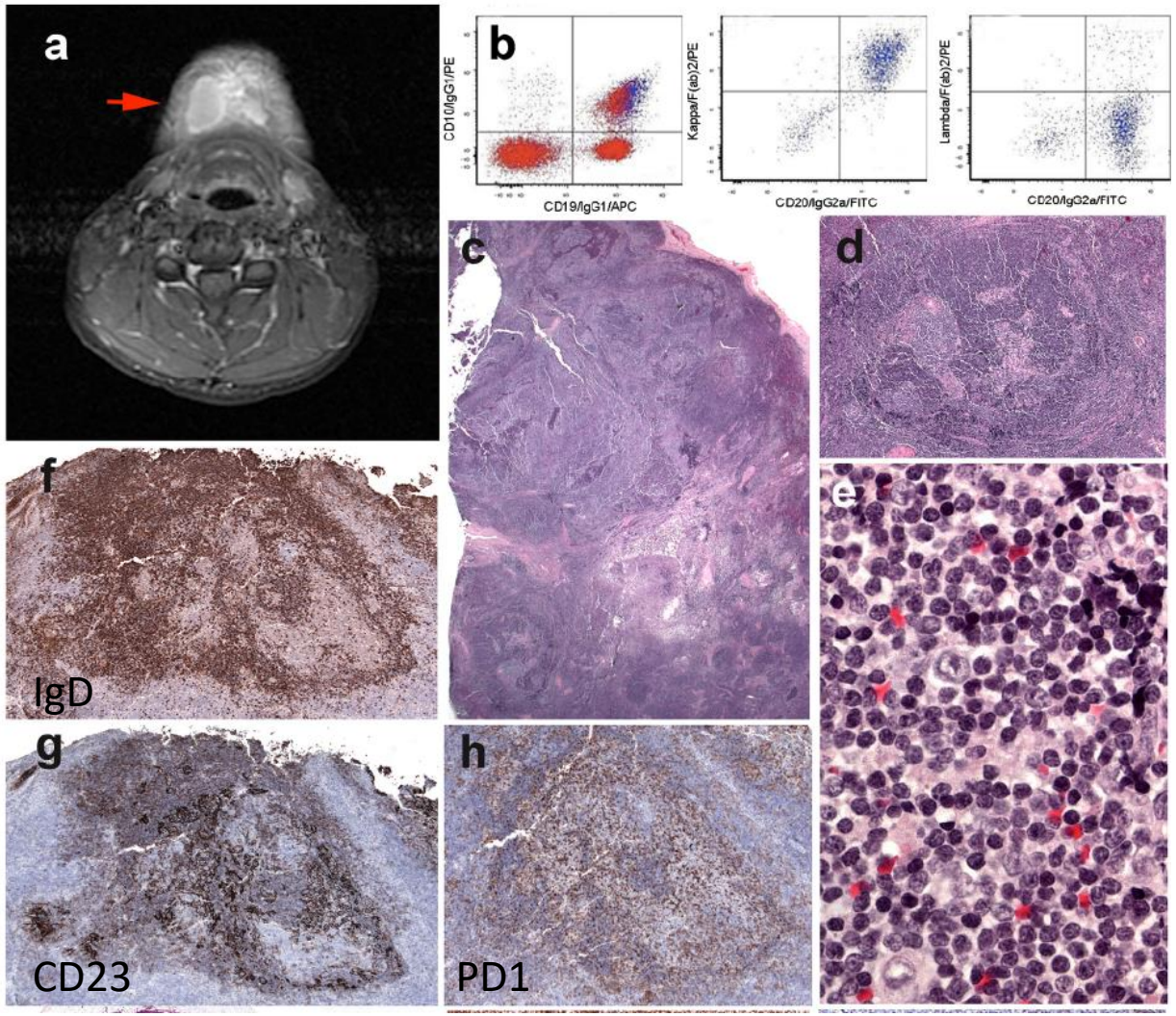
Taddesse-Heath et al, Am J Surg Pathol 2003;27:522

Pediatric nodal marginal zone lymphoma

Clinical history: 20-year-old man with a 2.1 cm submental lymph node. Asymptomatic 5 years only with excision.
Flow: 24% CD19+/CD10+/Kappa+ cells
IHC: Interfollicular cells are CD79a+, CD10 -, PTGC-like features and increased PD1+ cells in the follicles.

PTFL or PNMZL: What is your diagnosis ?

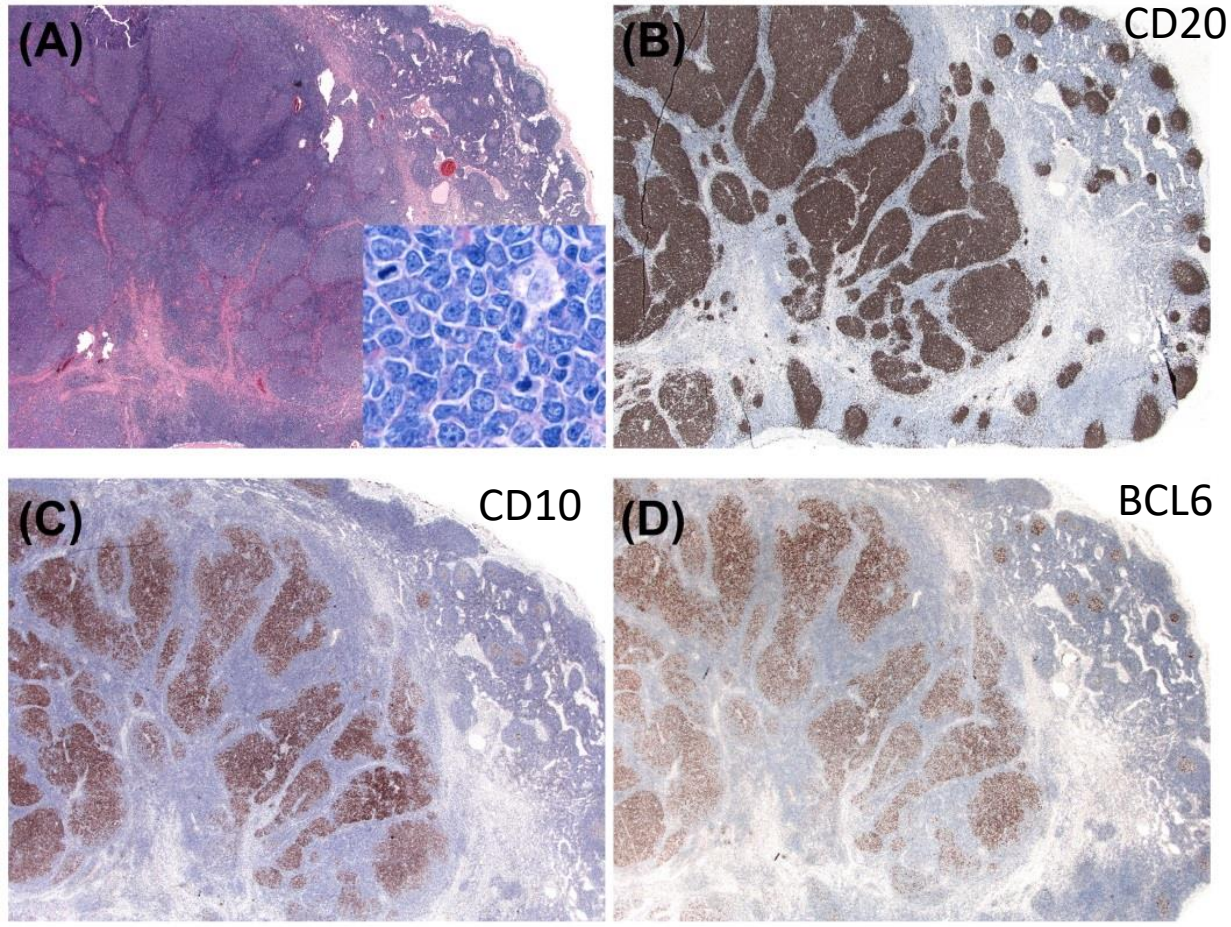
- Pediatric nodal marginal zone lymphoma with aberrant expression of CD10?



Quintanilla-Martinez L et al, Virchow Archiv 2015

Pediatric-type follicular lymphoma

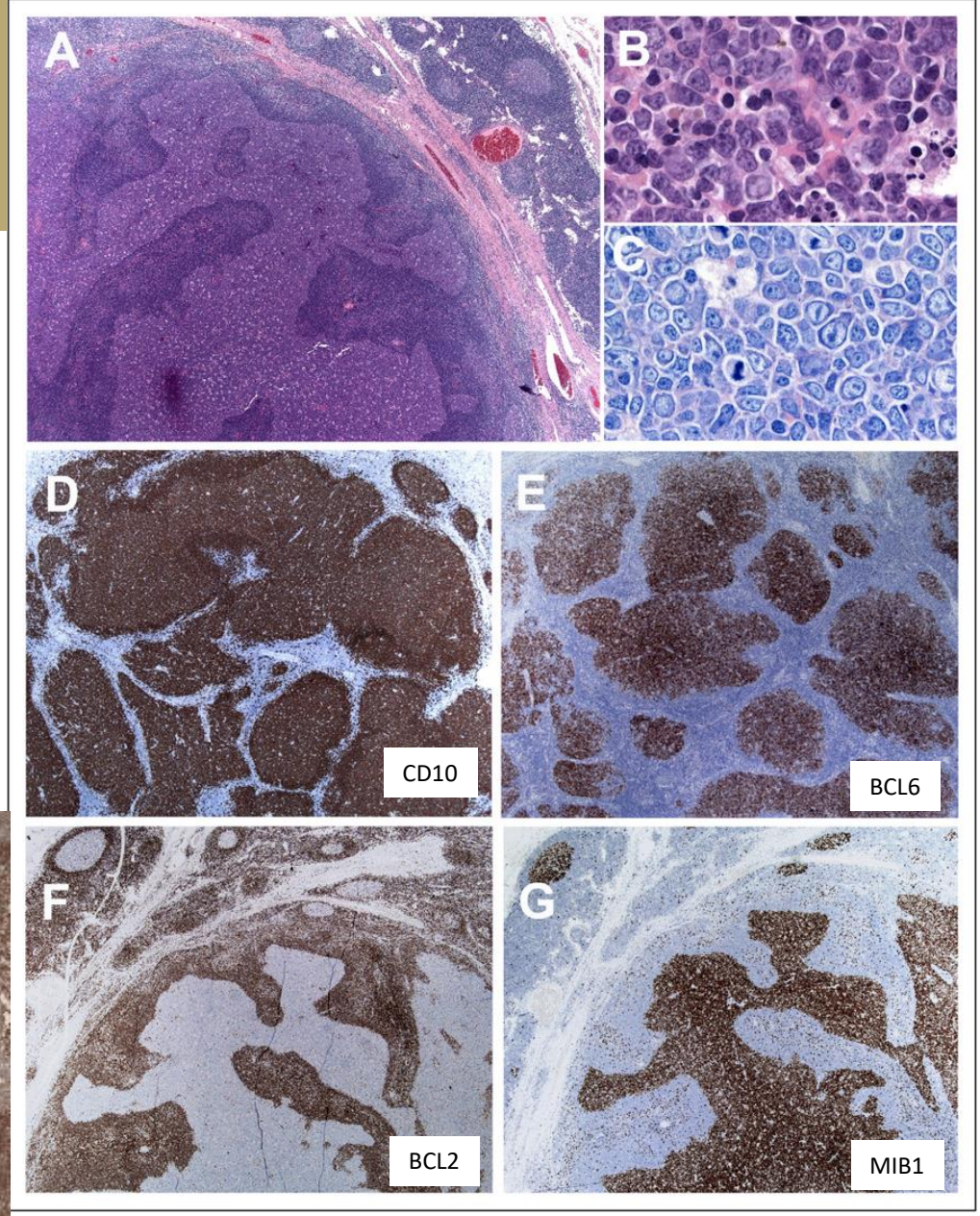
- Clinically:
  - Predominantly in male patients
  - Predilection head/neck LN
  - Early stage disease (I-II)
  - Good prognosis (watch & wait)
- Morphologically:
  - grade 3
  - Large, expansile serpiginous GC follicles
  - Lack of BCL2 expression
- Genetically:
  - no t(14;18)
  - Clonal analysis requiered!
    - IGH monoclonal



Liu Q et al, Am J Surg Pathol 2013; 37:33

Pediatric-type follicular lymphoma

- A „node within a node“ morphology
- Hifh grade cytology with starry sky pattern
- Strong CD10 and BCL6 expression
- BCL2 negative
- MIB1 high proliferation without polarization

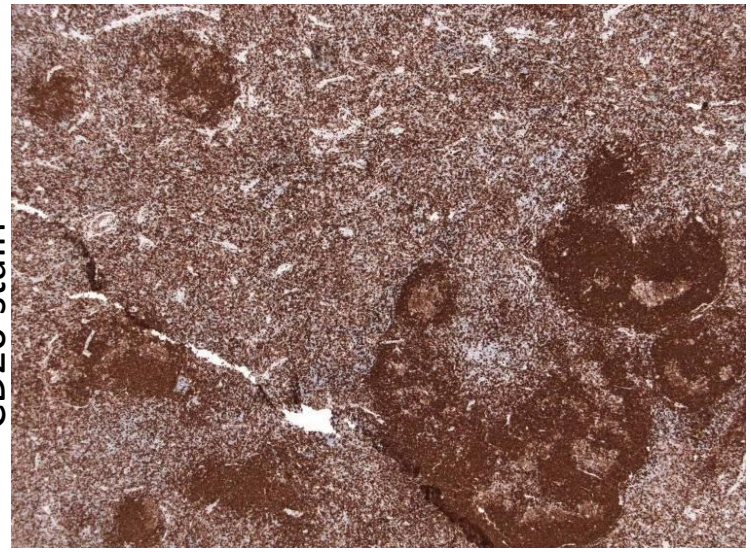


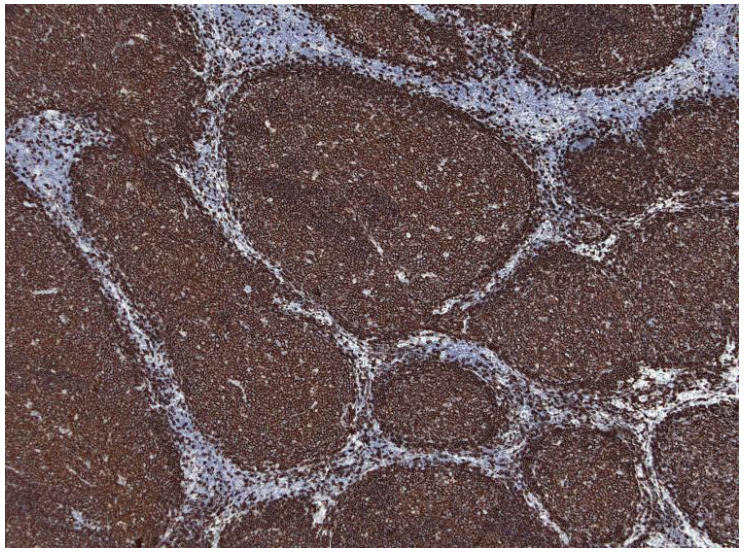
SCHMIDT et al BLOOD, 25 AUGUST 2016 • VOLUME 128, NUMBER 8

PNMZL

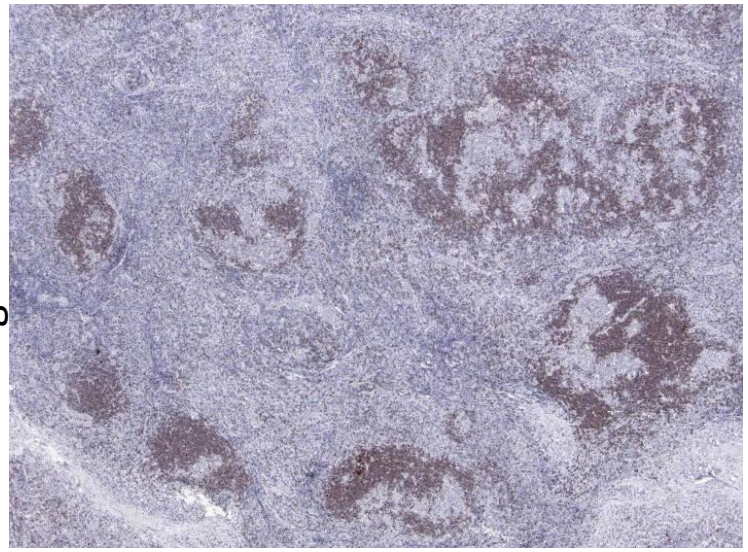
PTFL

CD20 stain





IgD stain



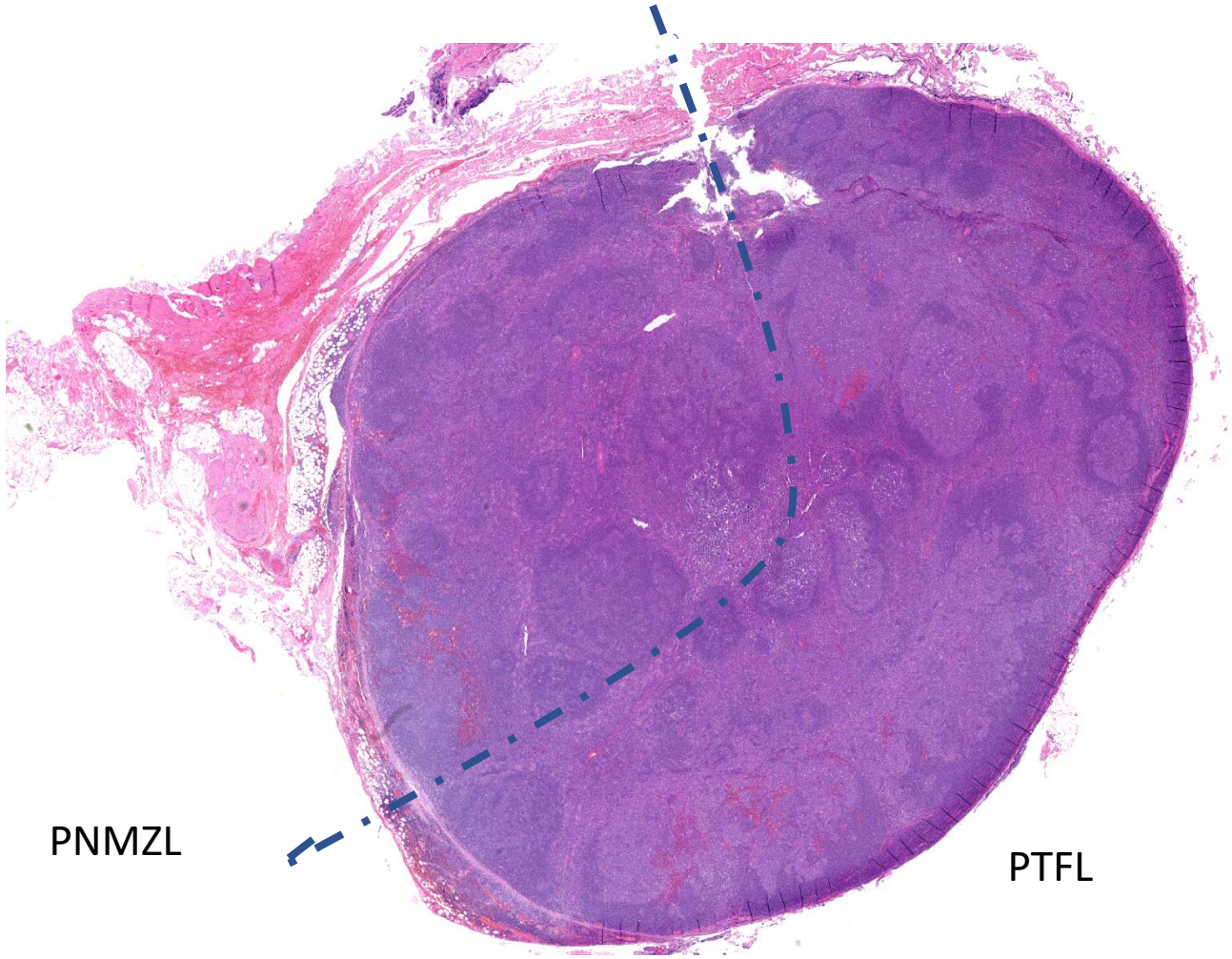
PTGC-like features

Serpigeneous GC with attenuated MZ

	Nodal FL (range)	NMZL (range)
Median age	14 years (5-21)	16 years (6-22)
M:F	20:1	20:1
Stage at presentation	100% localized	100% localized
Head and neck predilection	yes	yes
Diffuse areas	rare	often
PTGC	no	yes
Starry-sky pattern	yes	often
CD20 interfollicular	rare	yes
CD10+	100%	Rare
BCL2+	rare § (18%)	yes §
BCL6+	yes (100%)	No
CD279/PD1+	few/normal	increased

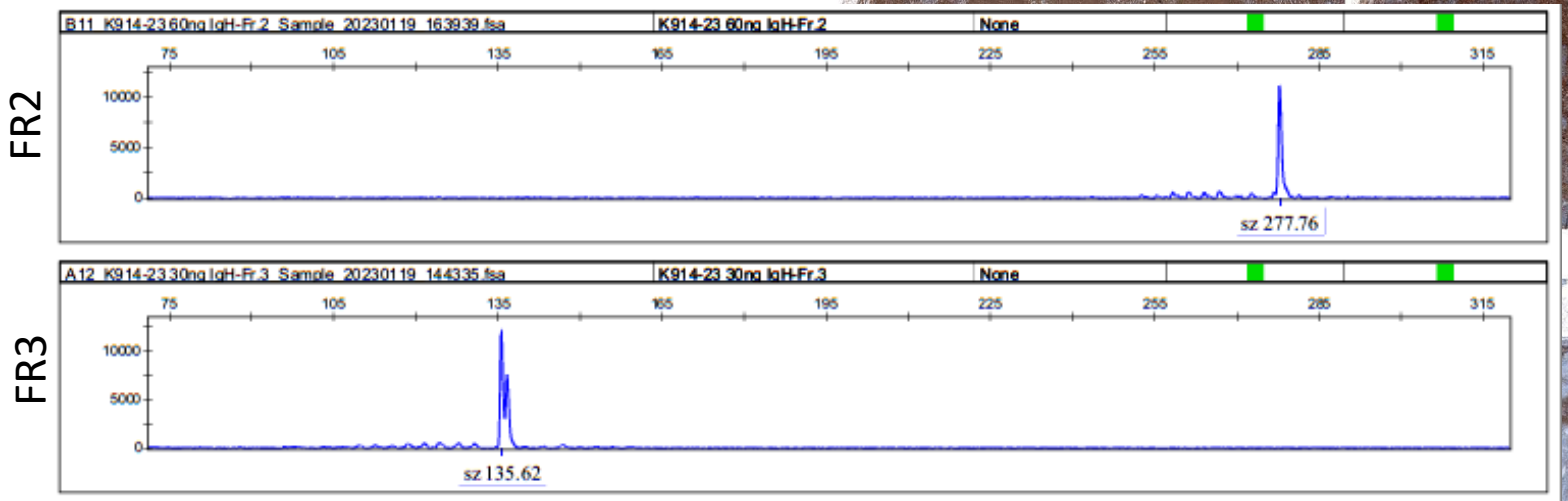
Follicular hyperplasia?, PTGC?

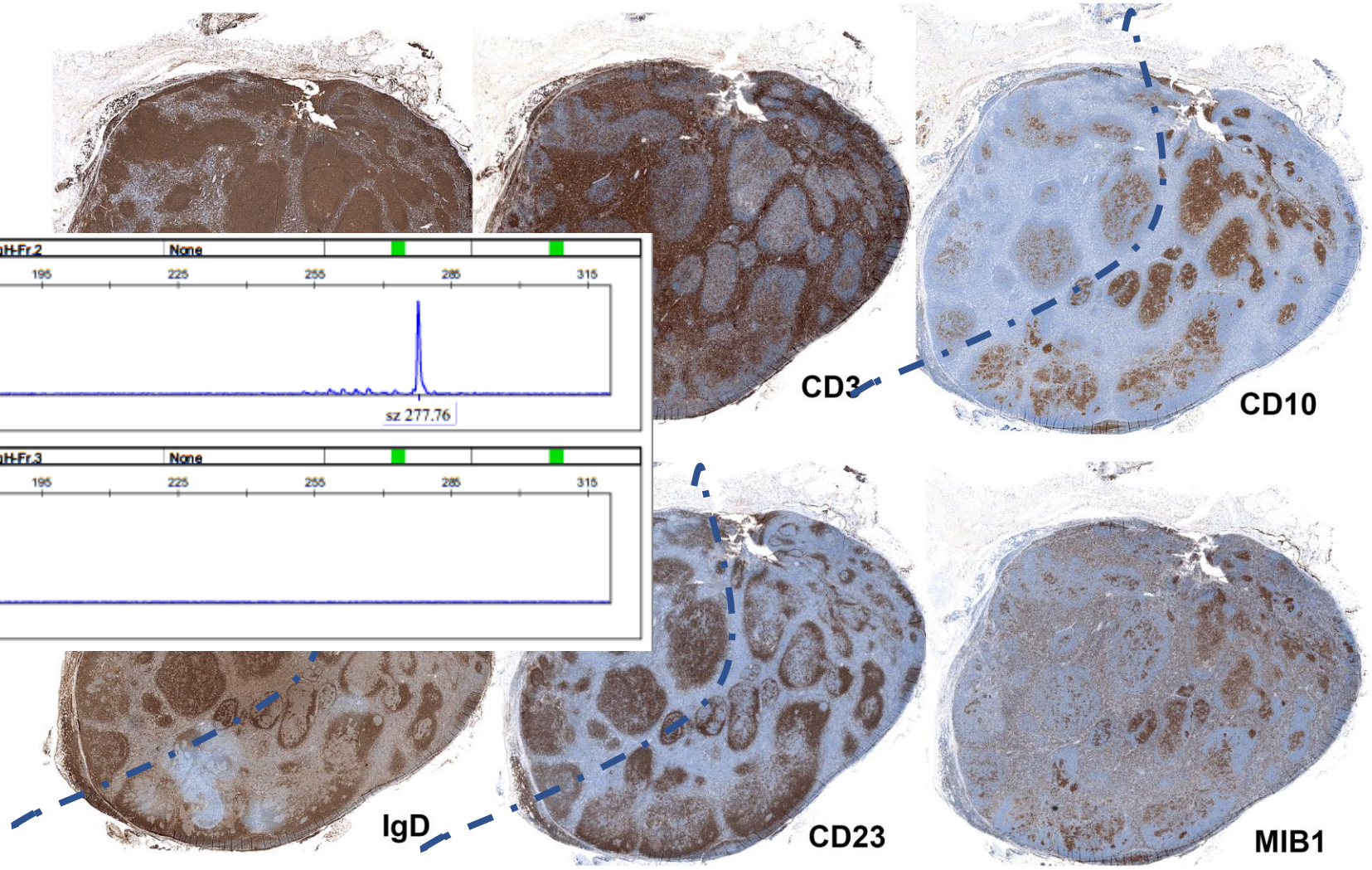
- 17 year-old female patient with enlarged retromandibular lymph node



Pediatric-type follicular lymphoma
with marginal zone differentiation

- Altered lymph node with a mixture of expanded germinal centers and PTGC





Universitätsklinikum Tübingen

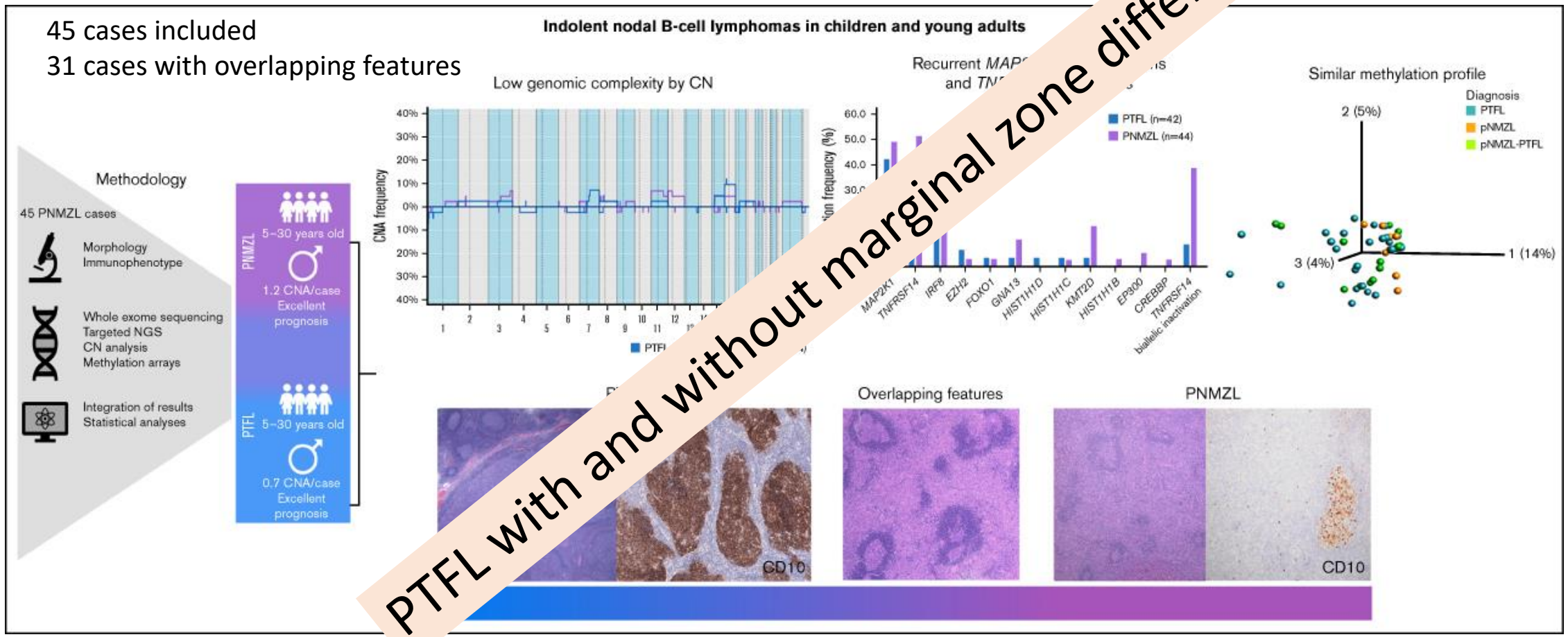
A unifying hypothesis for PNMZL and PTFL: morphological variants with a common molecular profile

Julia Salmeron-Villalobos,[1,2,*] Caoimhe Egan,[3,*] Vanessa Borgmann,[4,*] Inga Müller,[4] Blanca Gonzalez-Farre,[1,2] Joan Enric Ramis-Zaldivar,[1,2] Dominik Nann,[4] Olga Balagué,[1,2] Mónica López-Guerra,[1,2] Dolors Colomer,[1,2] Ilske Oschlies,[5] Wolfram Klapper,[5] Selina Glaser,[6] Young Hyeh Ko,[7] Irina Bonzheim,[4] Reiner Siebert,[6] Falko Fend,[4] Stefania Pittaluga,[3] Elias Campo,[1,2] Itziar Salaverria,[1,2,†] Elaine S. Jaffe,[3,†] and Leticia Quintanilla-Martinez[4,8,†]

23 AUGUST 2[illegible] NUMBER 16 blood advances

45 cases included

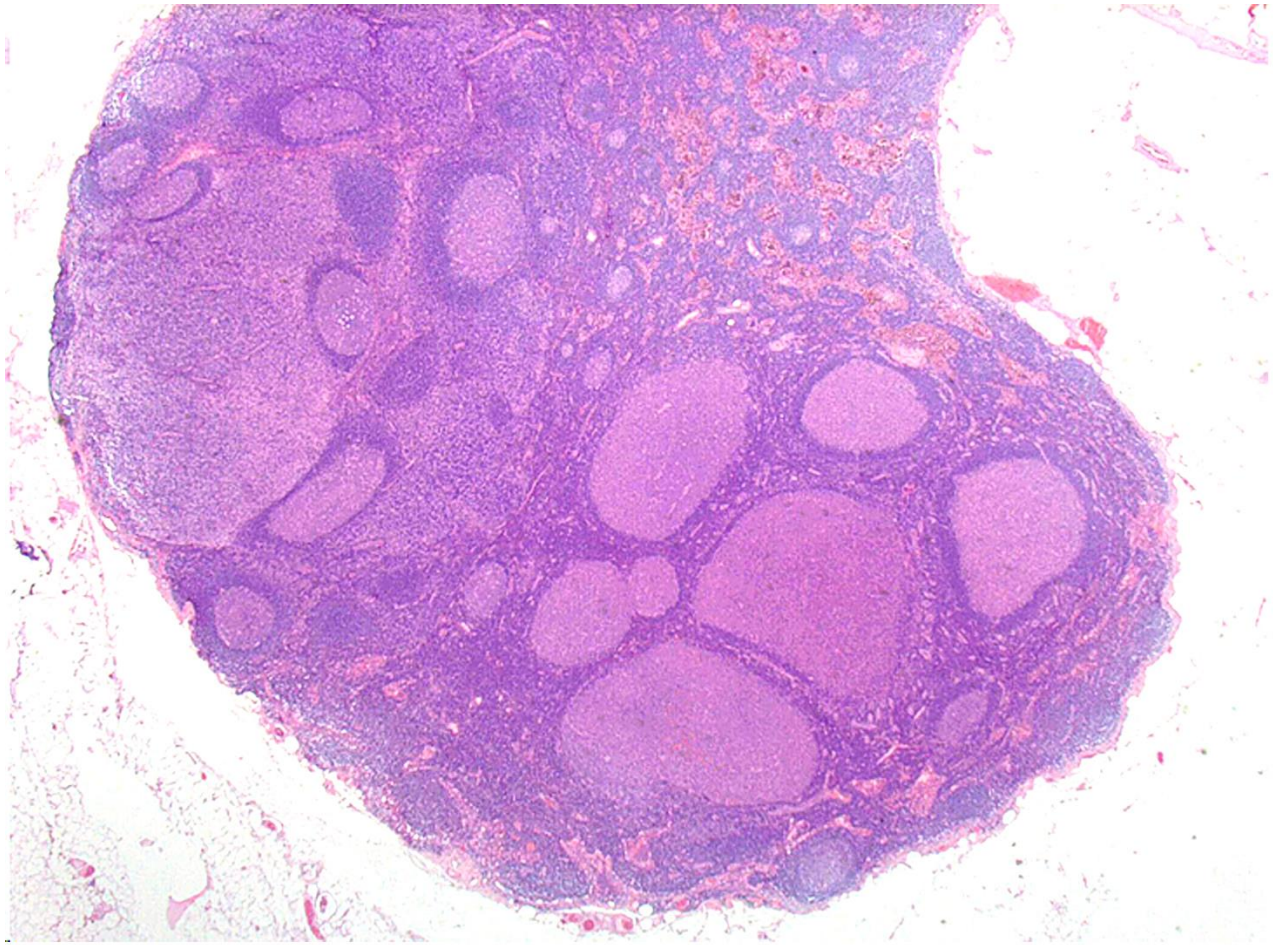
31 cases with overlapping features



PTFL with and without marginal zone differentiation

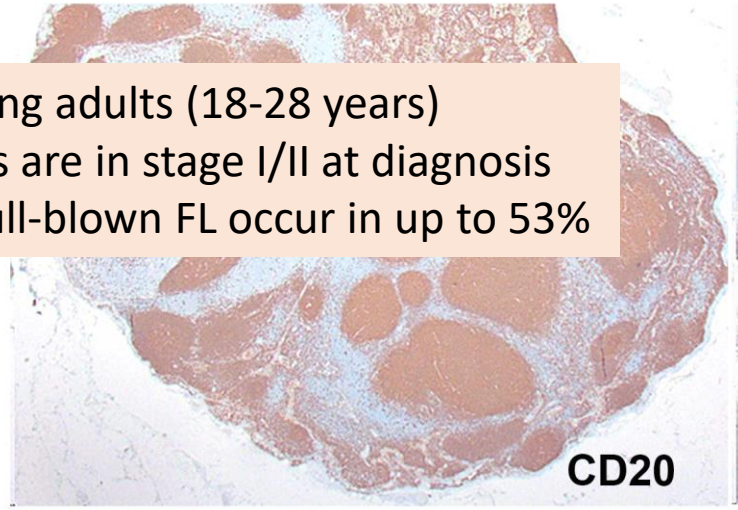
Reactive lymphadenitis?

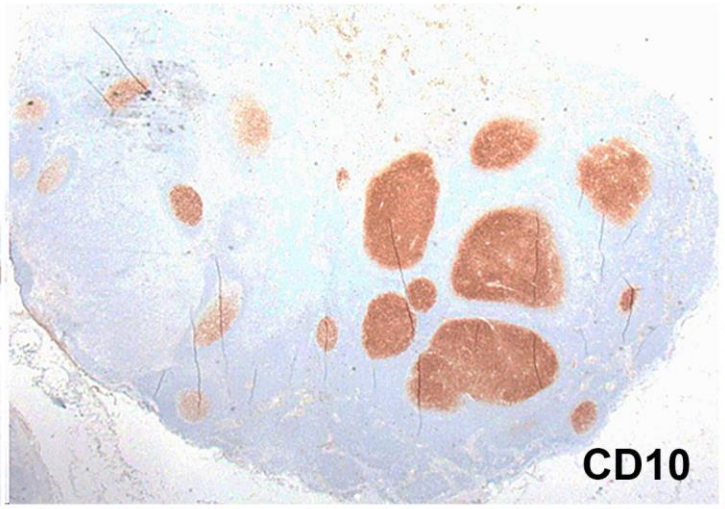
- 28-year-old female with cervical lymphadenopathy

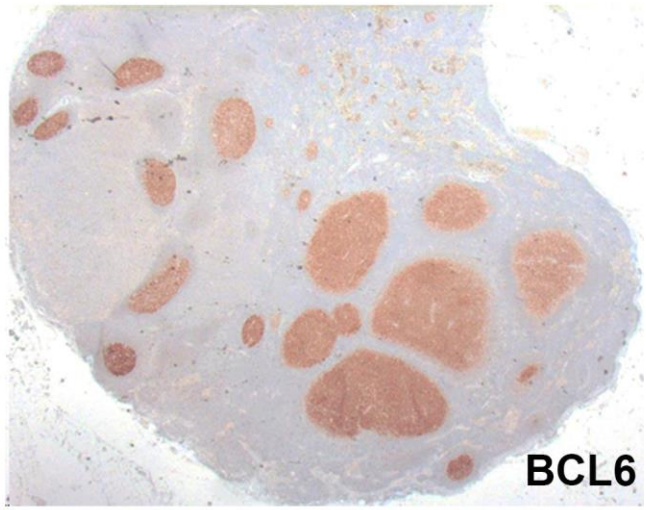


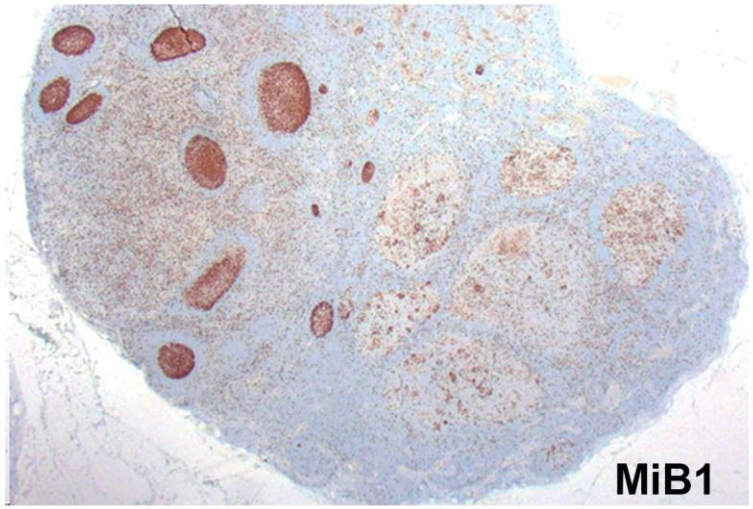
Partial involvement by cFL

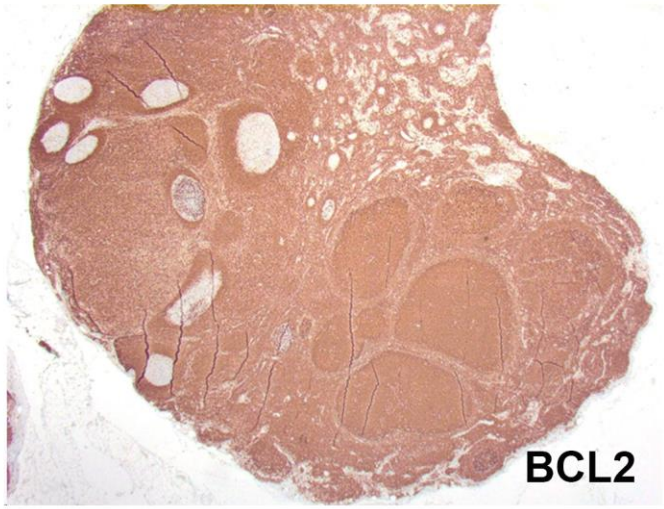
cFL do exist in young adults (18-28 years)
85% of these cases are in stage I/II at diagnosis
Progression to a full-blown FL occur in up to 53%

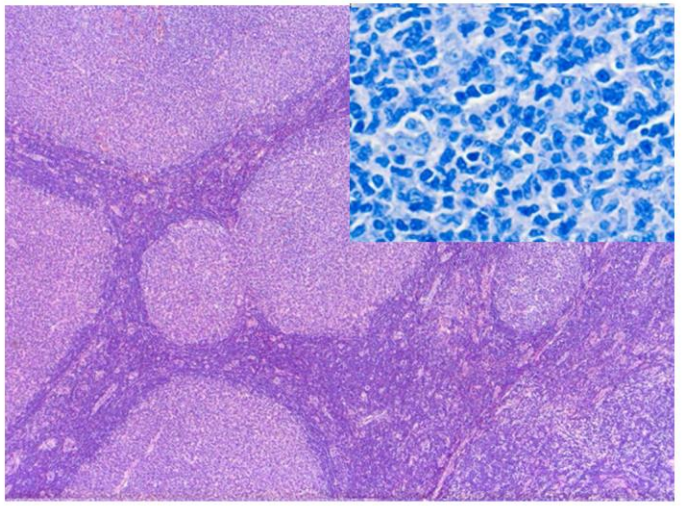






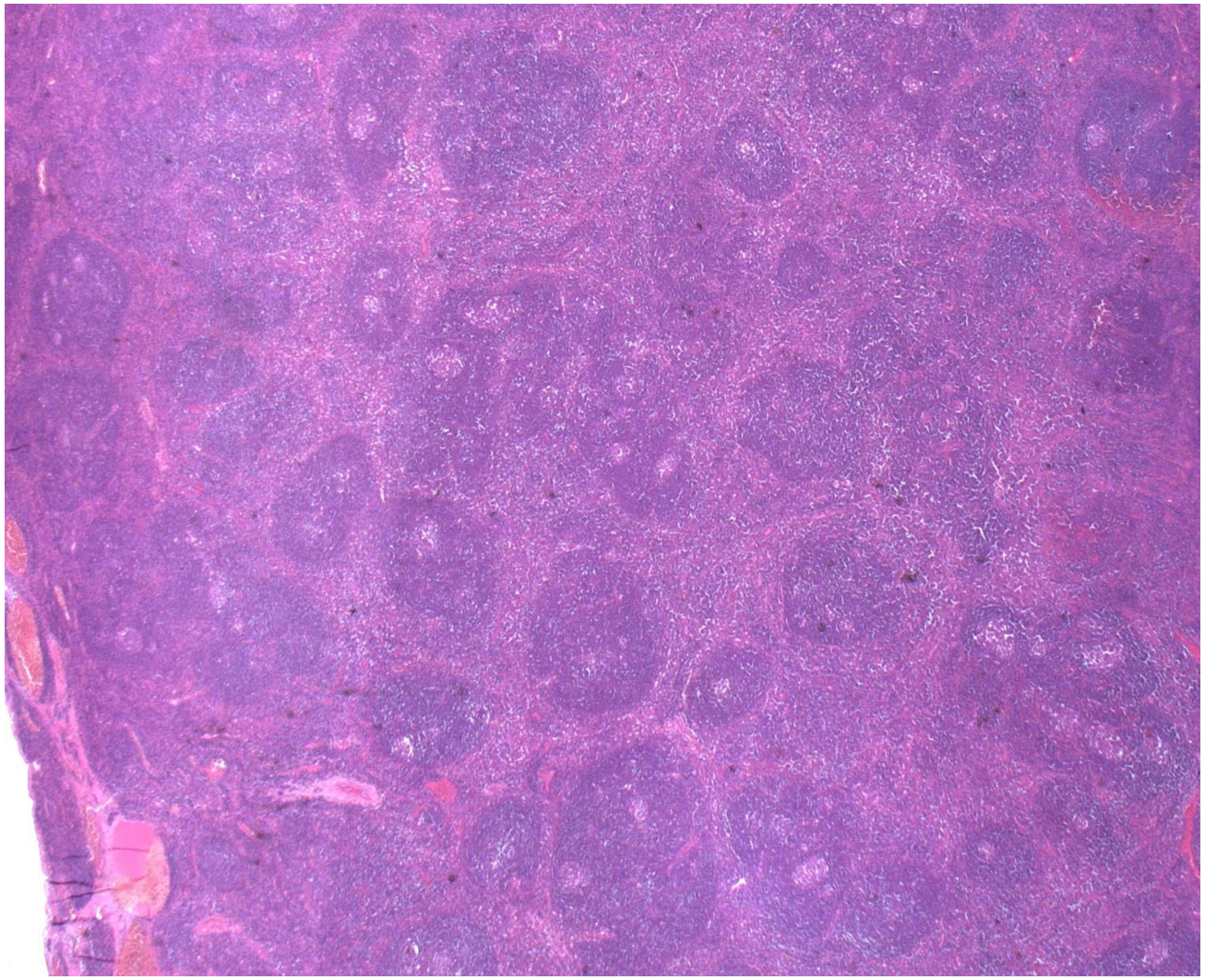






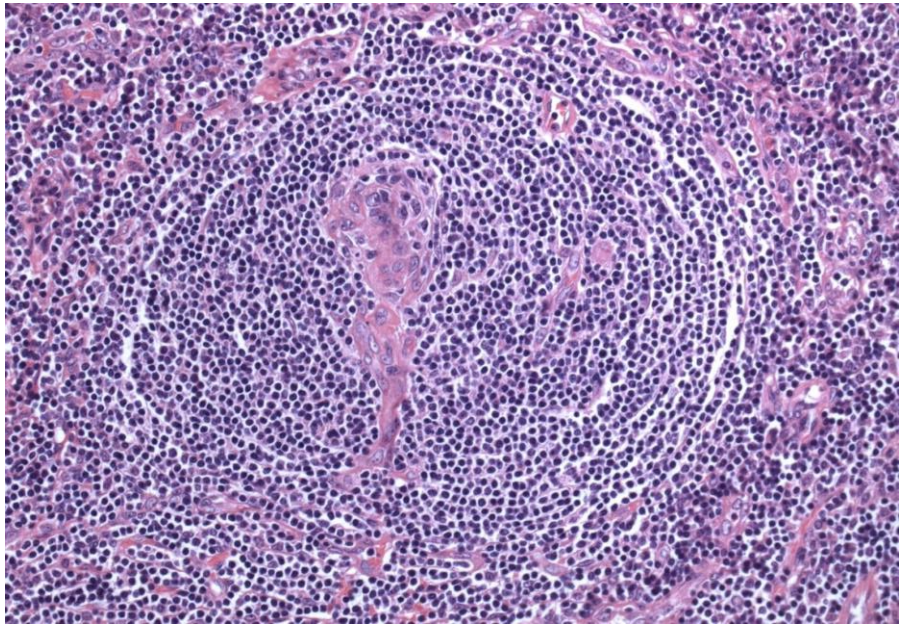
Follicular/nodular pattern

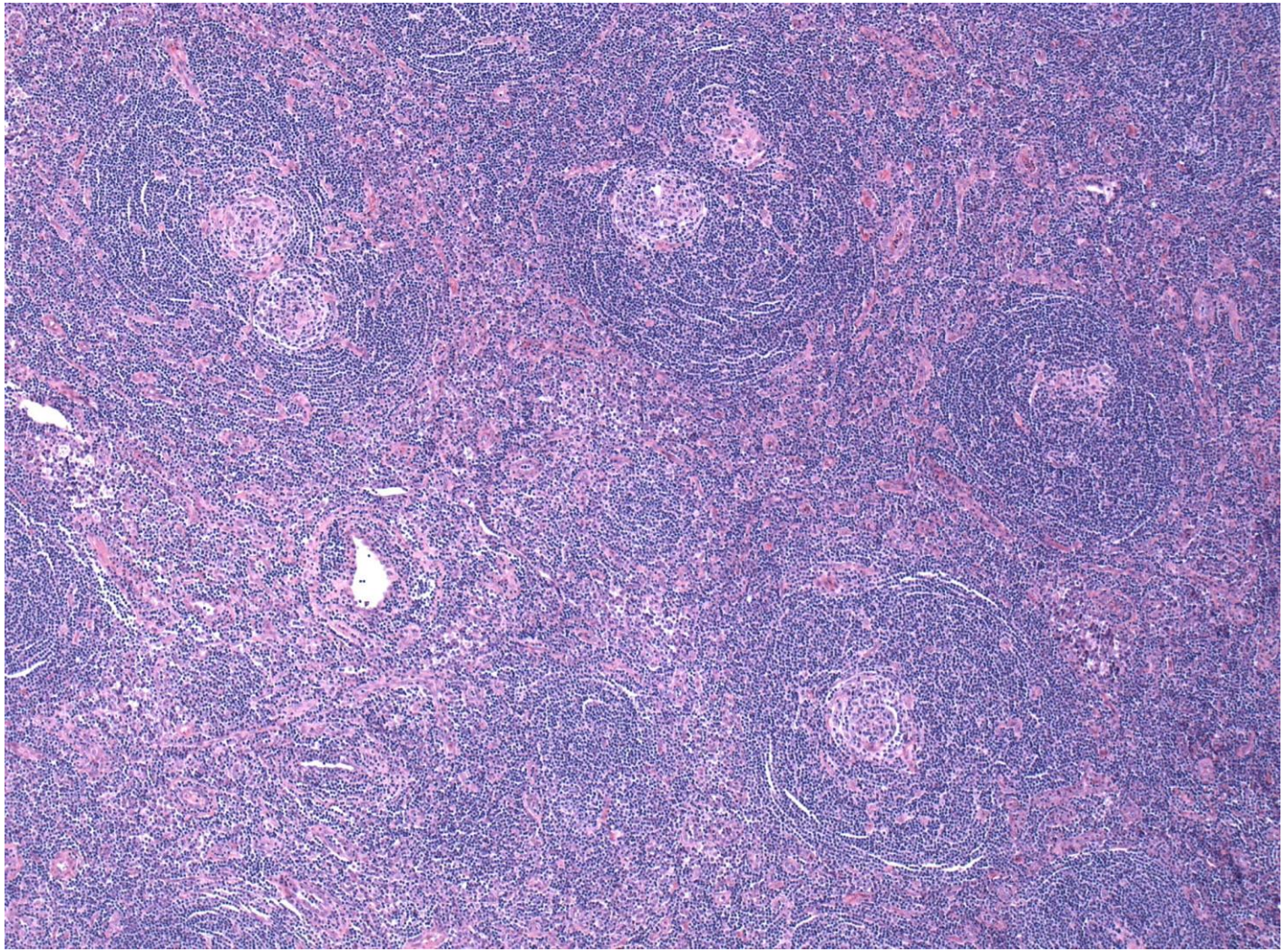
- 20-year-old male
- Increasing cervical lymphadenopathy over the last two years, otherwise healthy
- Status post *Borrelia* infection
- Whole body CAT scan: localized right-sided cervical lymphadenopathy, otherwise normal
- Lab findings: normal PB counts and differential, CRP, liver enzymes, LDH, β2-MG, total protein, electrolytes, etc. in normal range
- Excision of a cervical node 3.5x2.5 cm



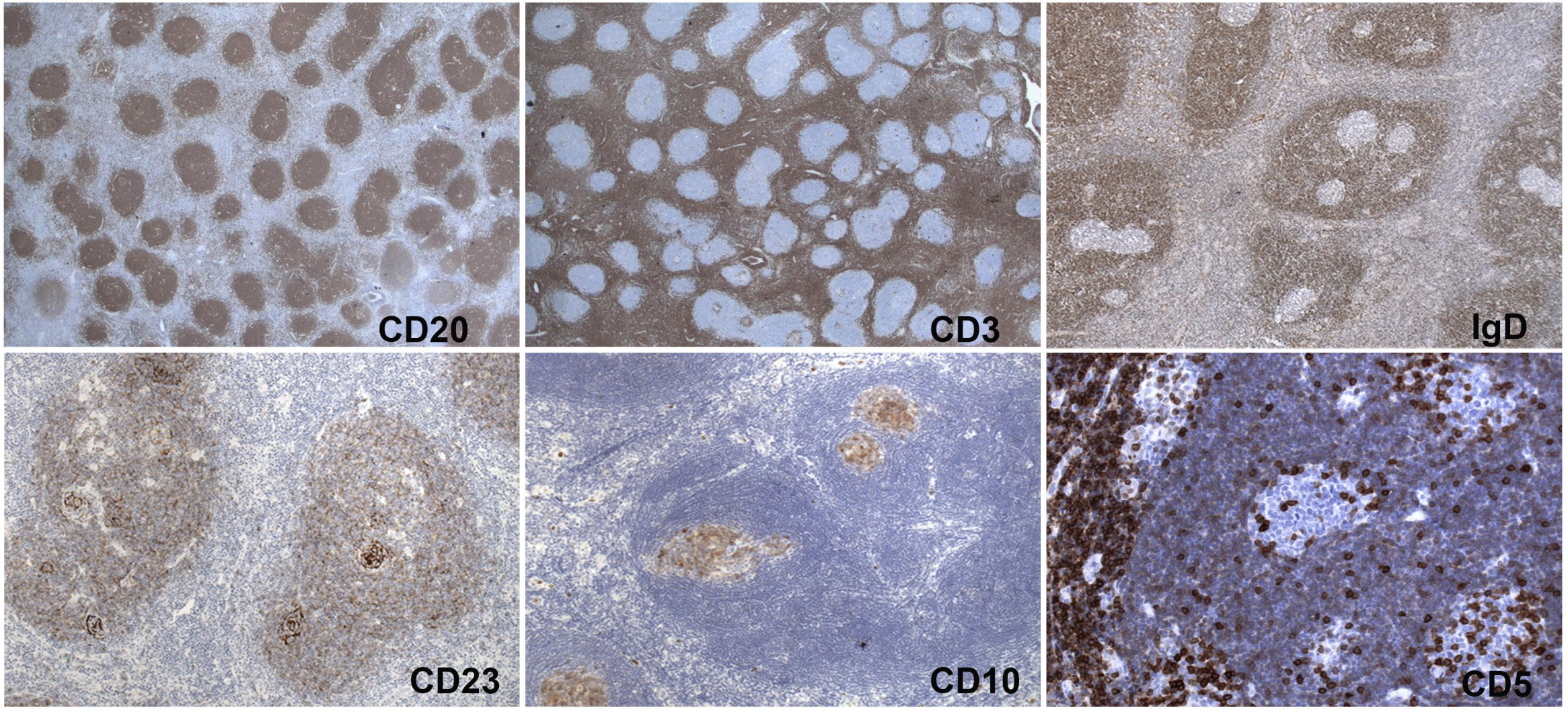
Castleman´s disease, Hyaline vascular type

- Increase number of follicules
  - Regressive germinal centers
  - Expanded mantle zone, tend to form concentric rings „onion skin pattern“
  - Blood vessels penetrate the GC „lollipop follicle“
  - Several germinal centers share the mantle zone
- Hypervascular interfollicular region





Castlelman´s disease, Hyaline vascular type
CD5 expression by follicular mantle cells



Interfollicular hyperplasia

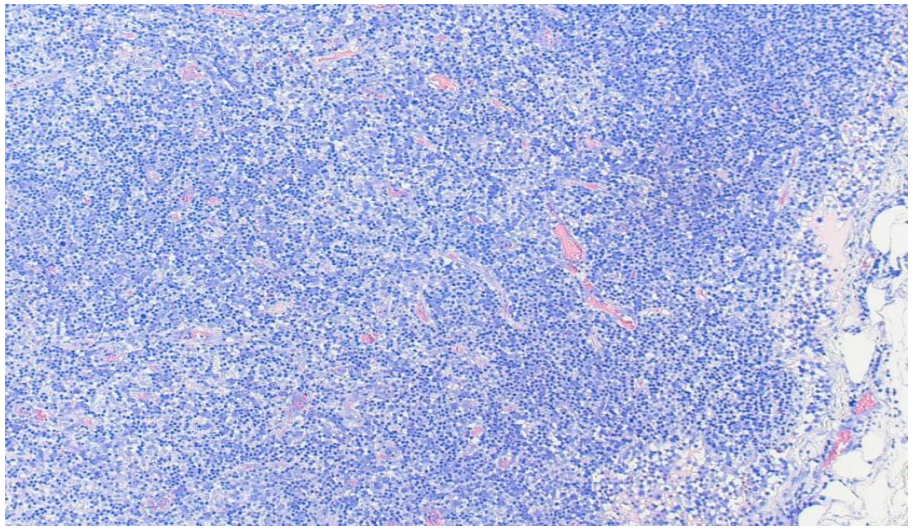
Morphology

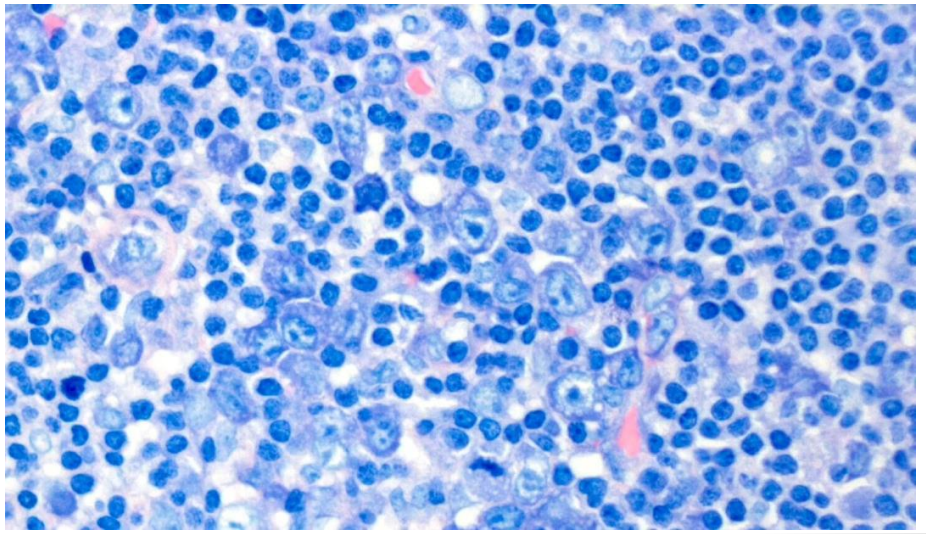
- with/without follicular hyperplasia, sometimes follicles reduced/depleted, monomorphic/ polymorphic (with plasma cells)

Immunohistochemistry

- B-immunoblasts (CD20 et CD79a+), usually MUM1+, T-cells, often many cytotoxic T-cells CD8+ and TiA-1+, polytypic plasma cells, frequent CD30+ blasts with variable intensity

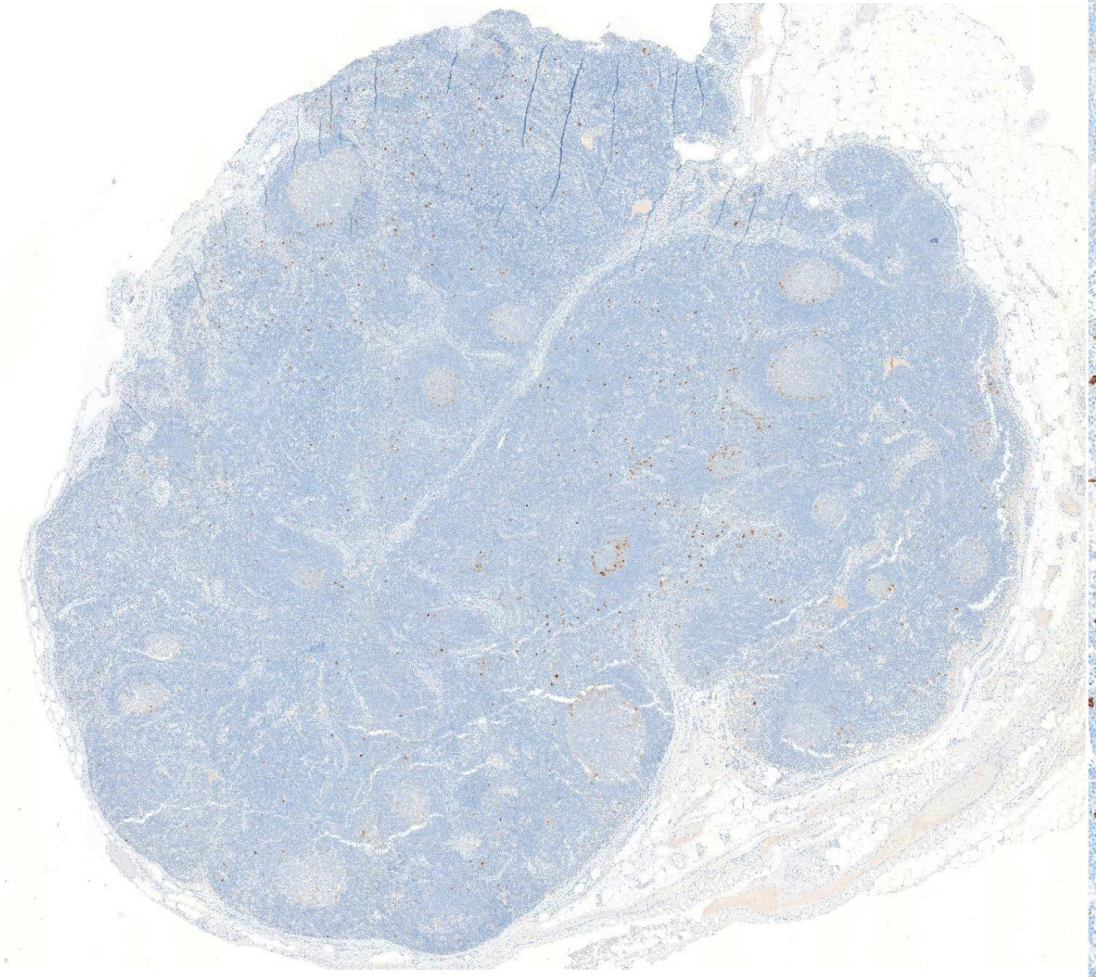
Viral infection, autoimmune disease

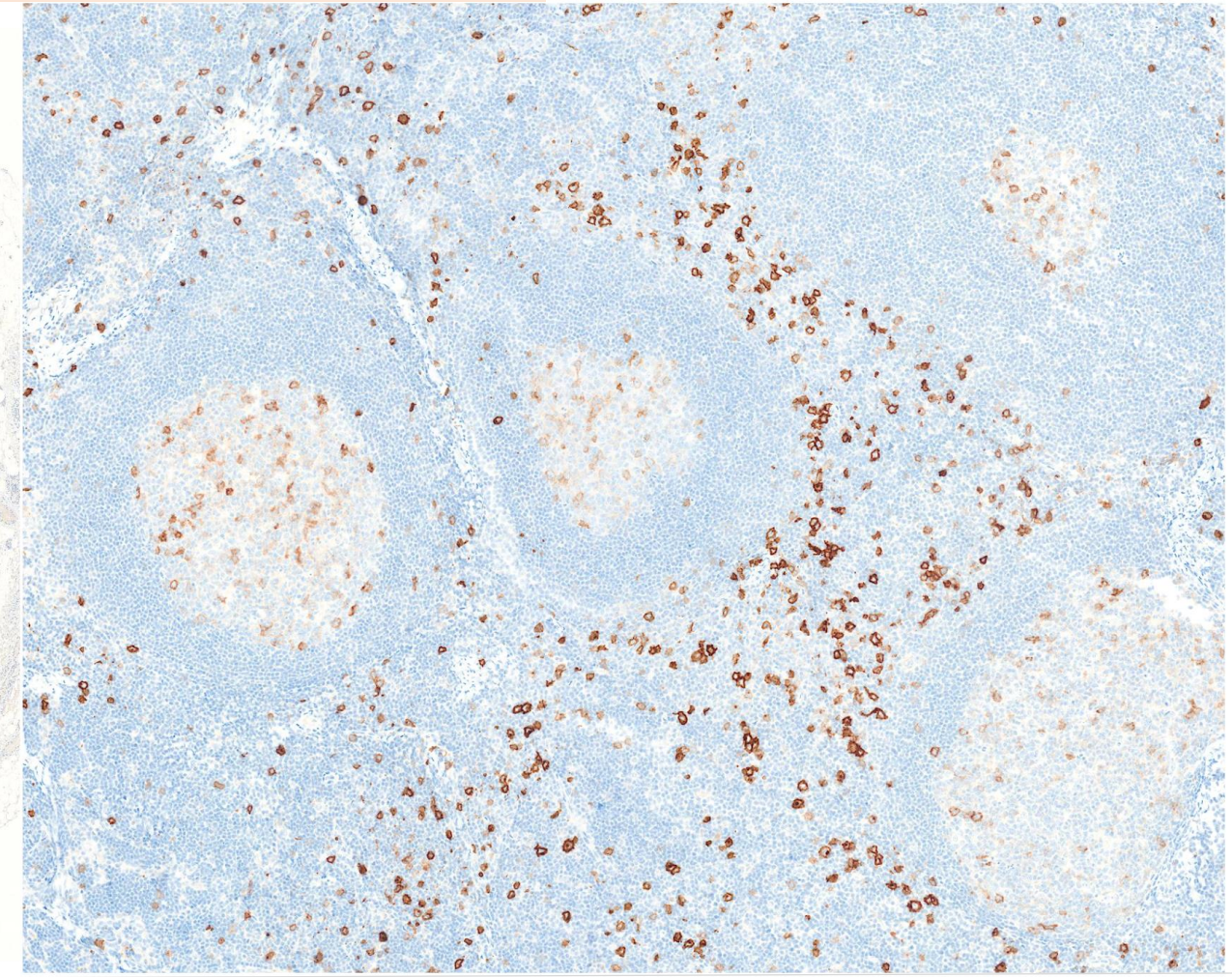




CD30+ reactive cells

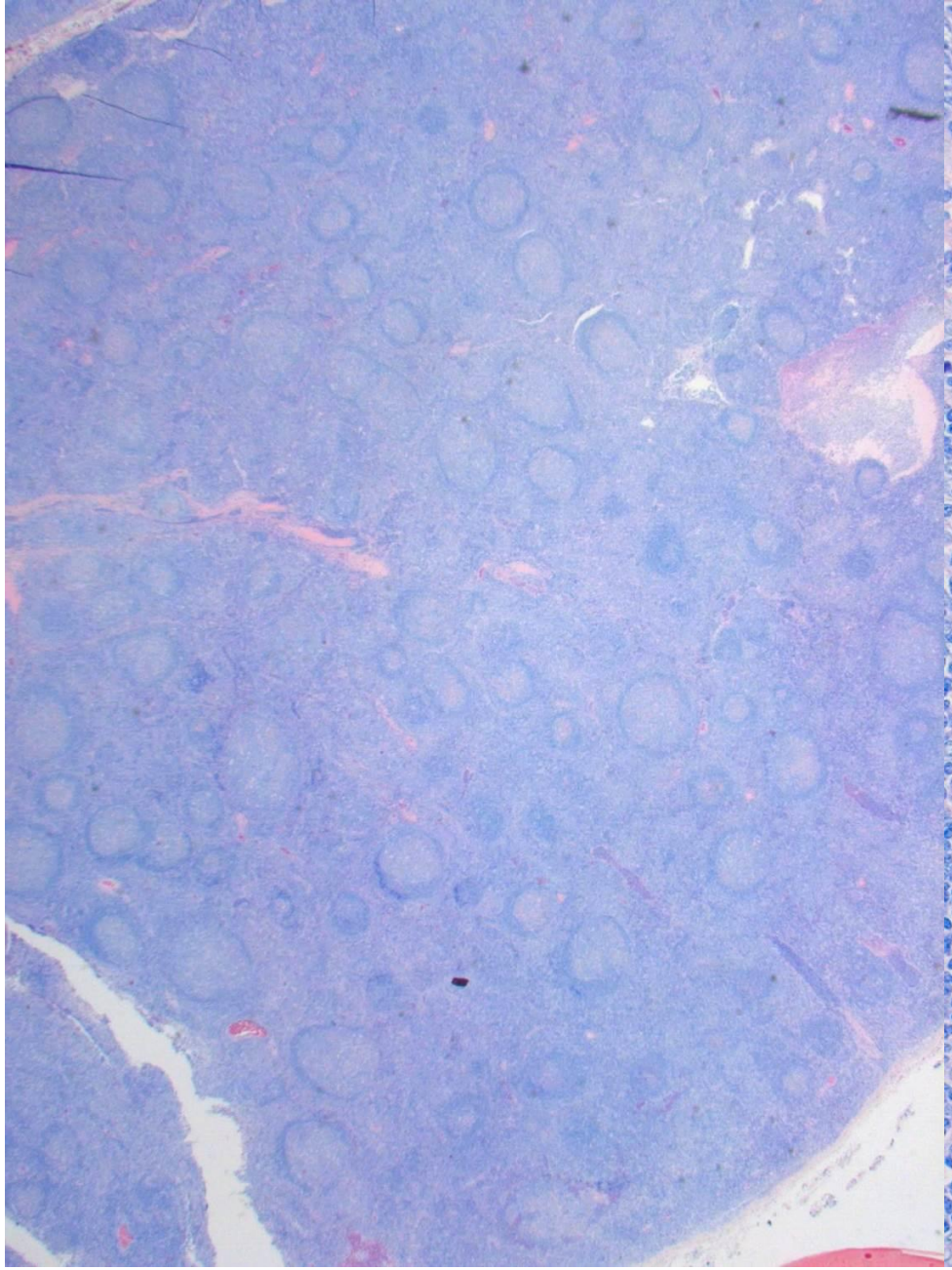
Usually intrafolllicular and perifollicular

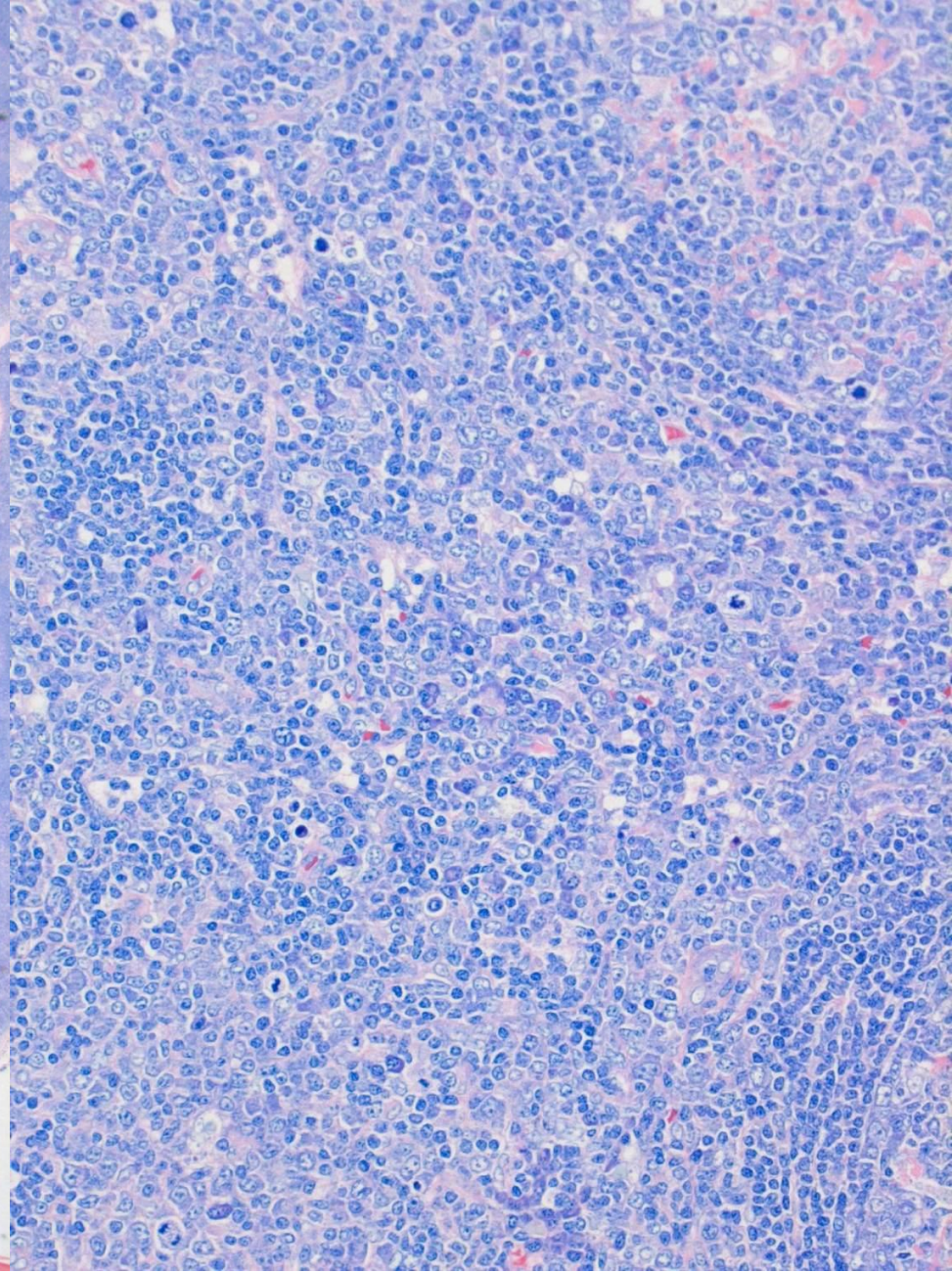




- 11-year-old male, with lymphadenopathy, a lymph node was excised.

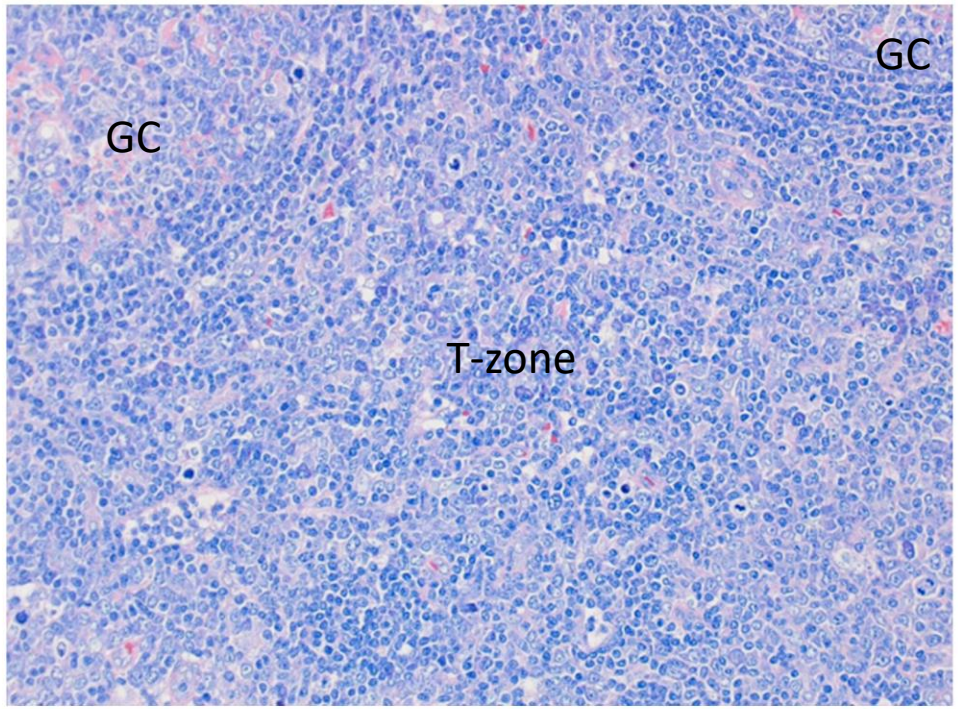
- Follicular hyperplasia with relatively small follicles and attenuated mantle zone
- Expanded polymorphic paracortical area

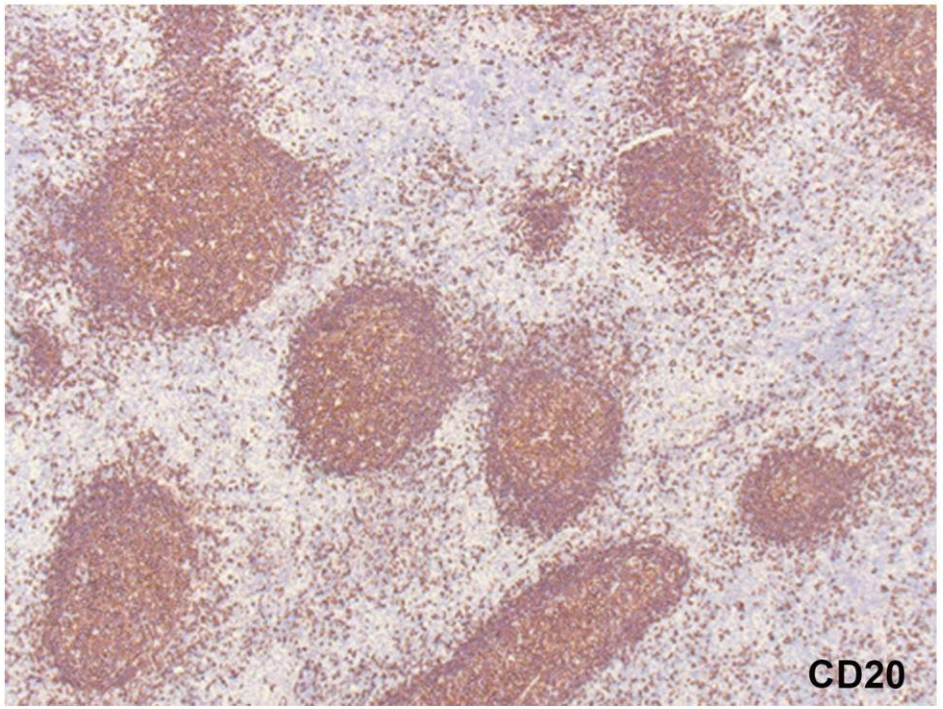


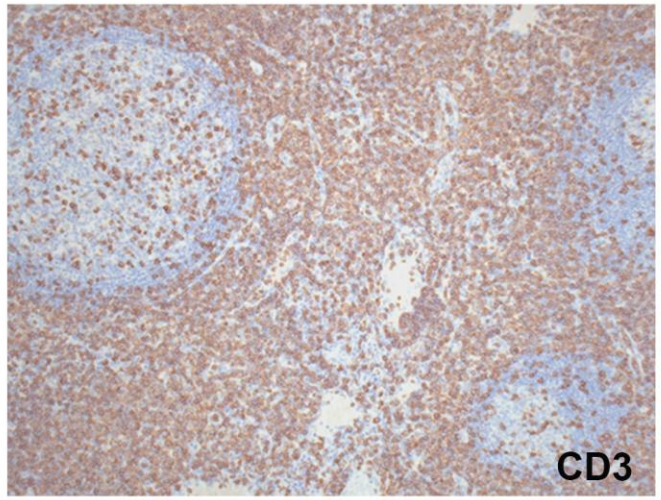


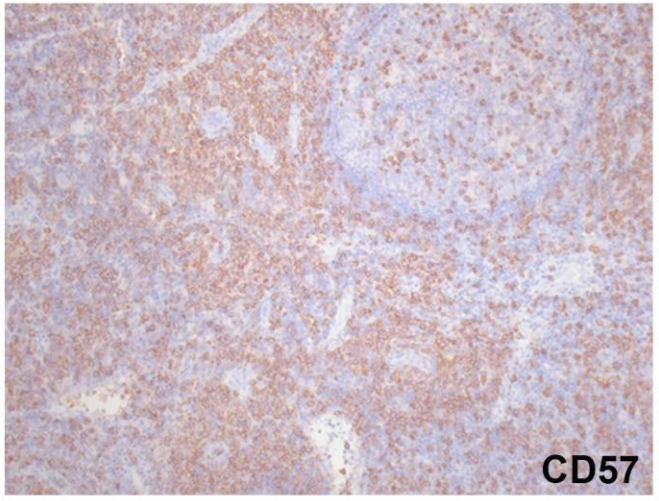
Autoimmune lymphoproliferative syndrome (ALPS)

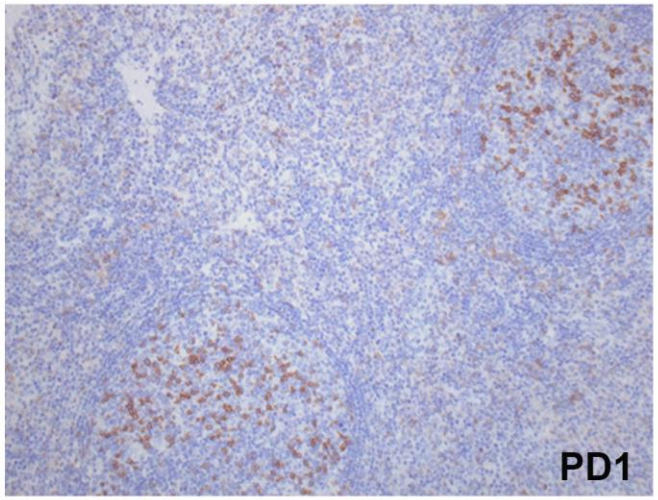
Double negative
CD4/CD8
CD3+CD57+ cells



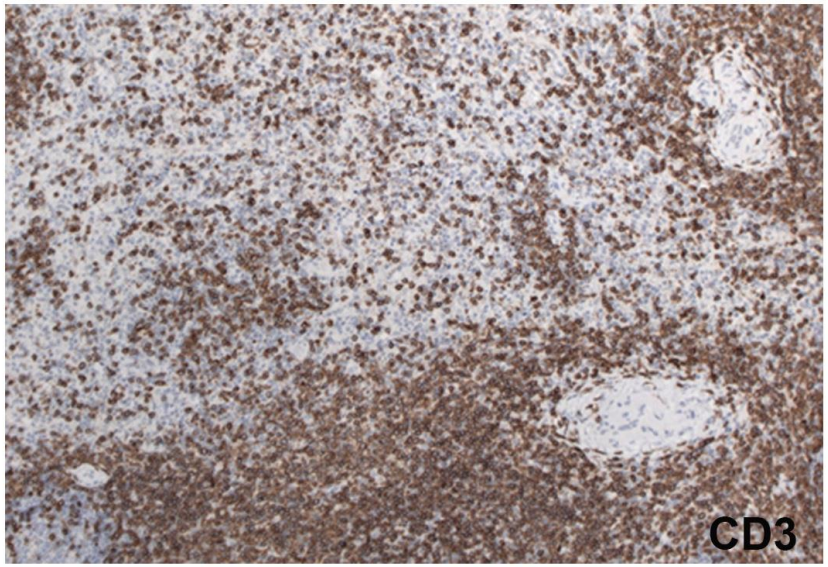


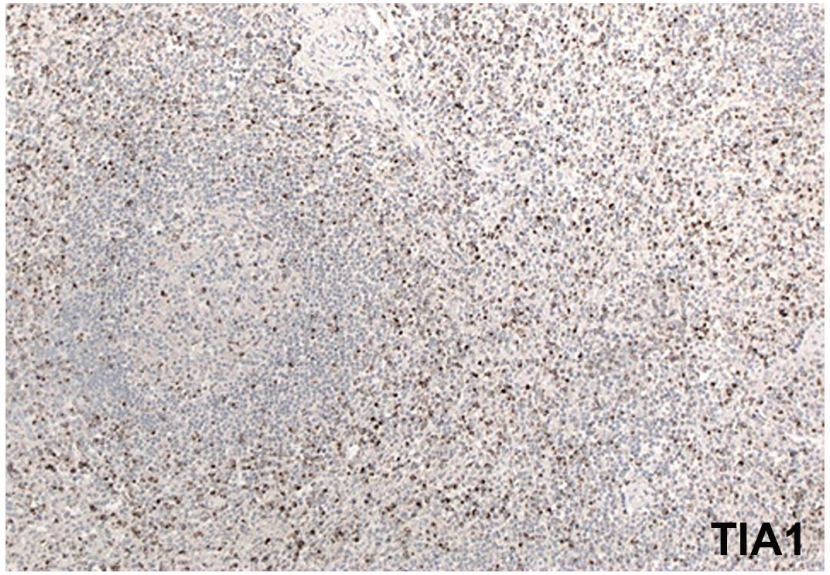


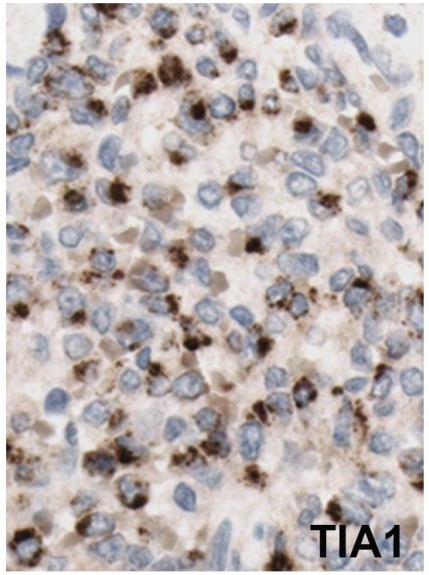


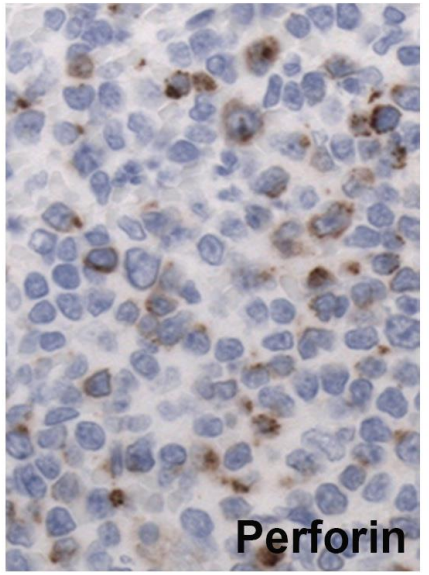


Autoimmune lymphoproliferative syndrome (ALPS)



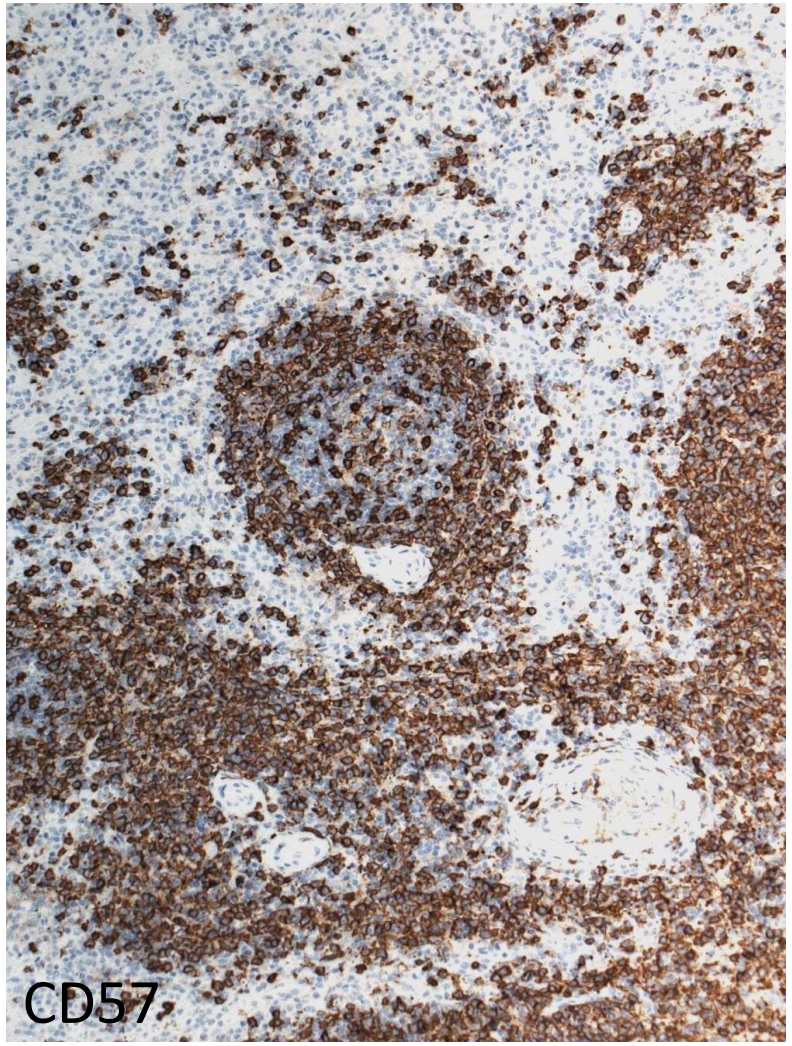


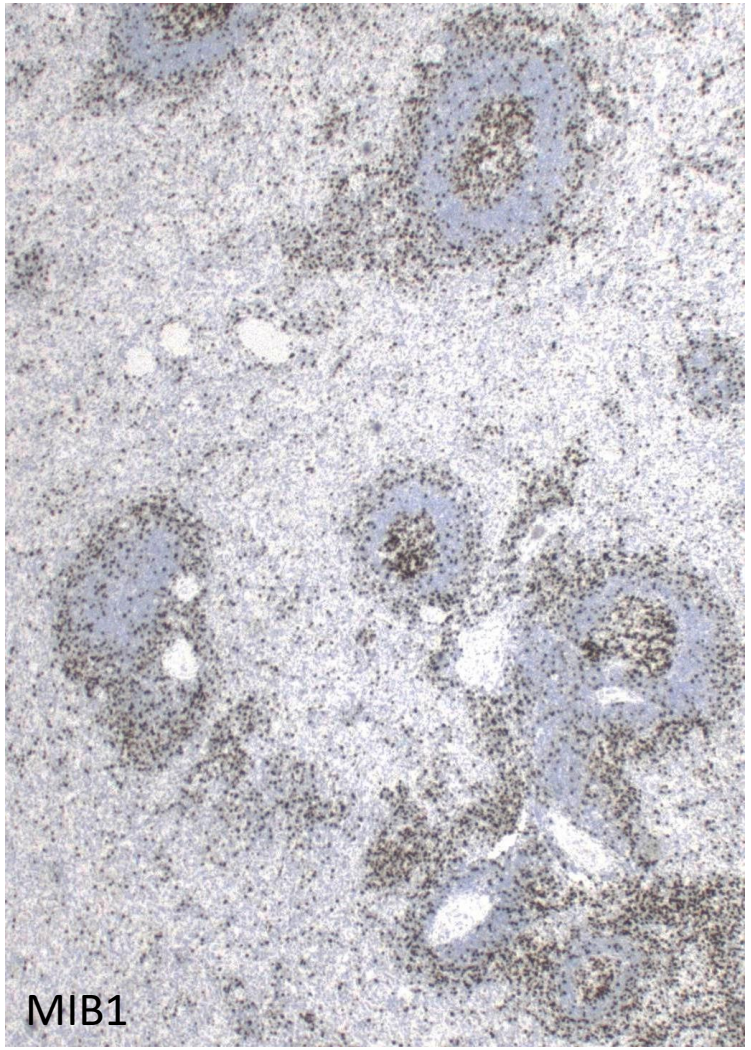


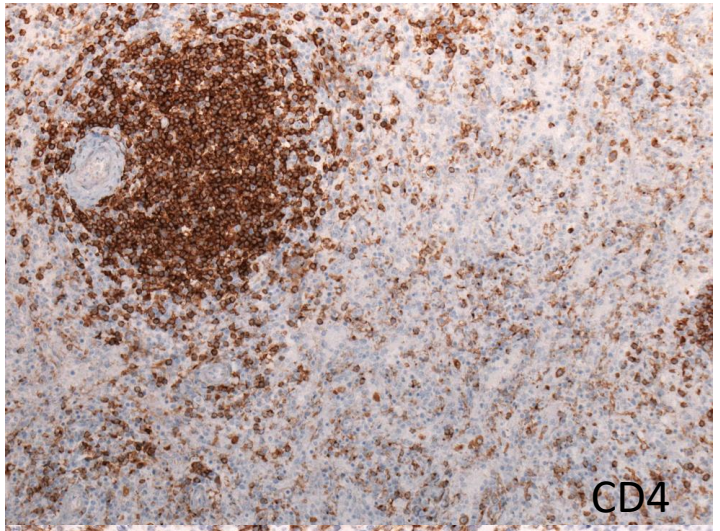


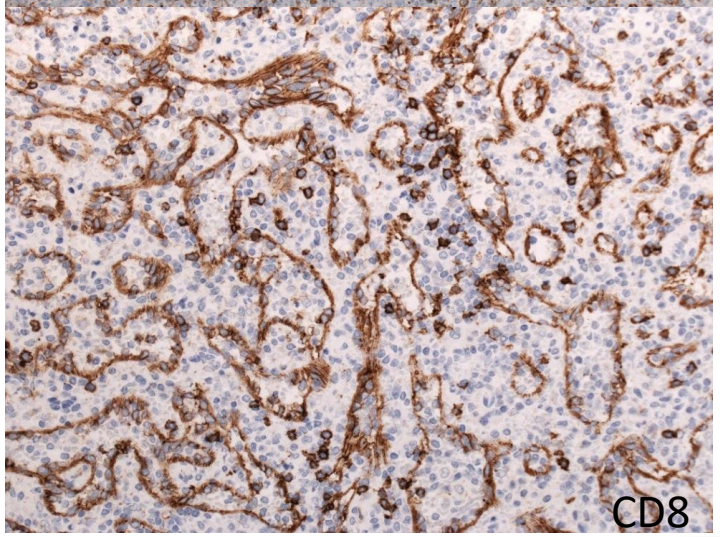
- Lymph nodes
  - Marked paracortical expansion with mixed infiltrate with high proliferation rate and decrease apoptotic bodies
  - Increased in DN T-cells with expression of cytotoxic markers (TIA++, Perforin+) and CD57+, CD45RO-, CD25-
  - CD4+ T-cells mainly in GC (TFH)
  - Florid follicular hyperplasia
  - Usually polyclonal B and T-cell rearrangements
  - Occassional PTGC or Castleman-Like GC

Autoimmune lymphoproliferative syndrome (ALPS)
Spleen

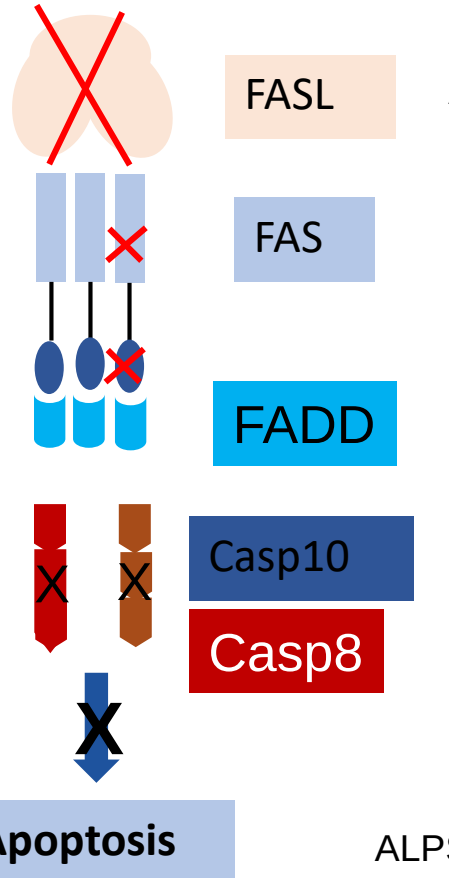








Autoimmune lymphoproliferative syndrome (ALPS)
Genetic basis and classification



ALPS-FASL (1b): 2%

ALPS-FAS (1a)
ALPS-sFAS (1m)
} Together 80%

ALPS-Casp10 (2a): 3%

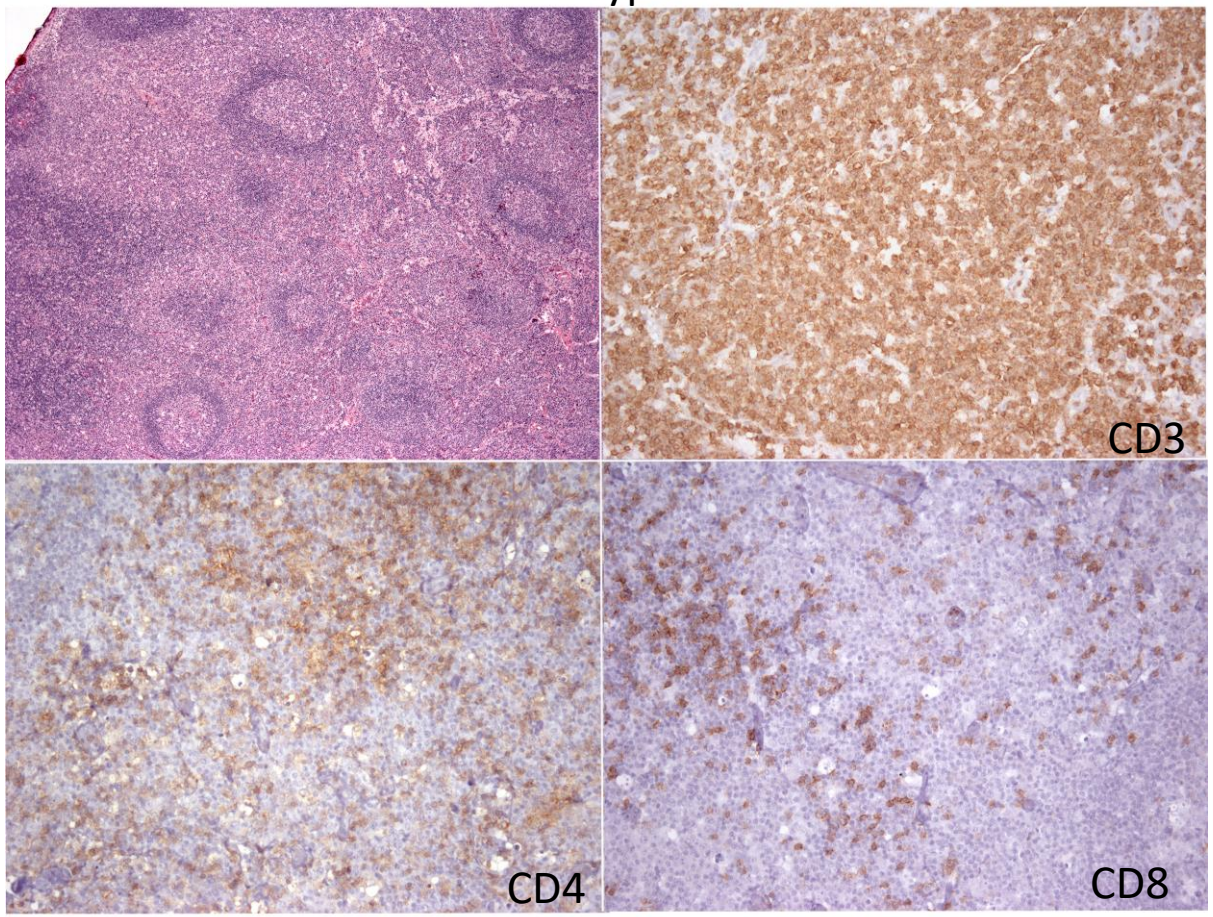
CEDS (2b): rare

ALPS-U (3): 10-15%, no known mutations

Fas pathway

Oliveira et al, BLOOD 2010

Atypical paracortical hyperplasia with DN T-cells
ALPS Type IA



Pittaluga S, Hematopathology Book, 2nd edition

Autoimmune lymphoproliferative syndrome (ALPS)

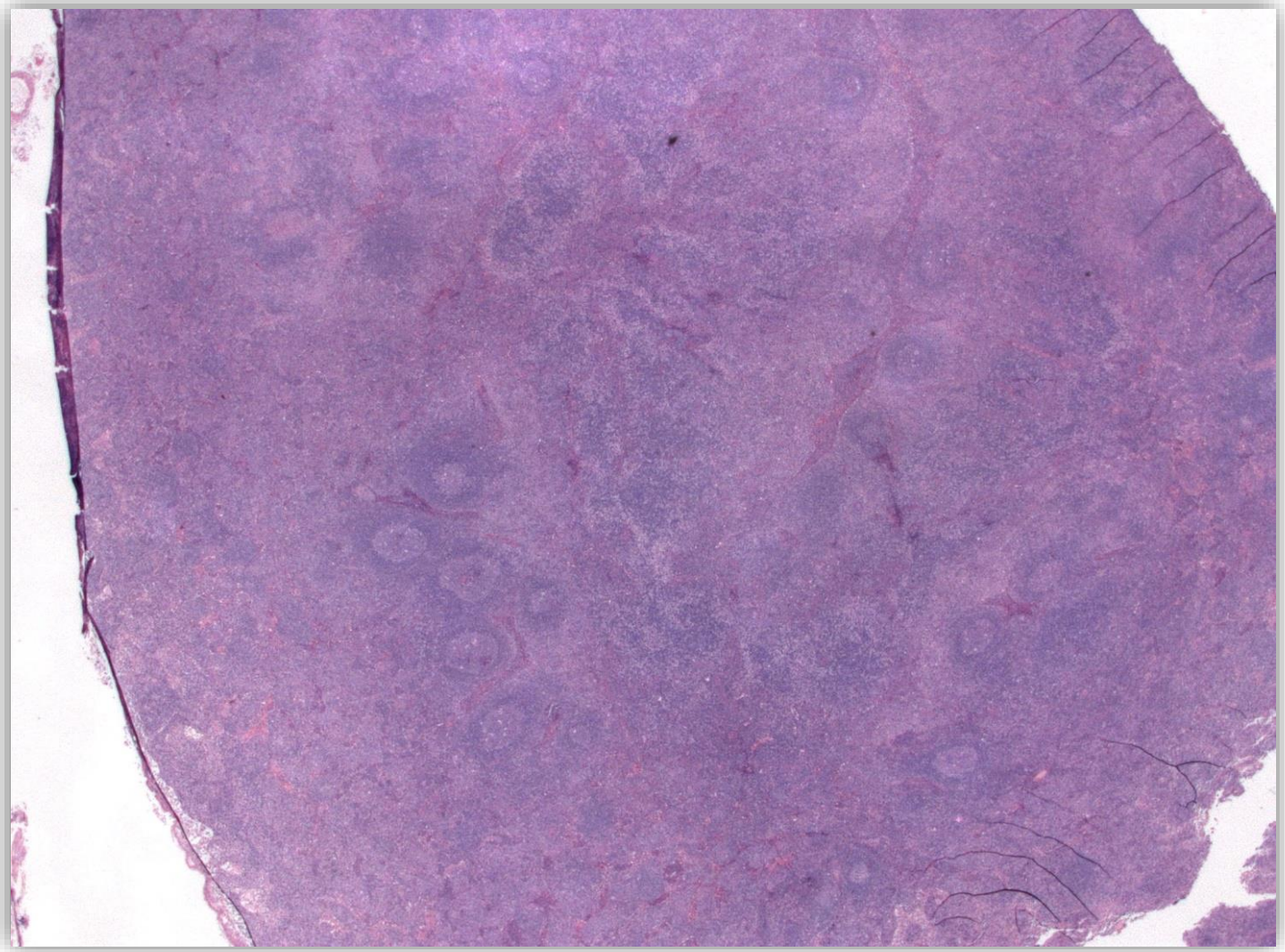
- Rare disorder with autosomal dominant inheritance
  - Usually diagnosed in childhood
- Lymphoid hyperplasia with accumulation of non-neoplastic lymphocytes
  - Generalized lymphadenopathy and hepato and/or splenomegaly
- Autoimmune phenomena
  - Hemolytic anemia, thrombocytopenia
  - hypergammaglobulinemia
- Increase in CD4/CD8 double negative T-cells CD57+
- Significantly increased risk for B-cell NHL and CHL.

- Required diagnostic criteria
  - Chronic (>6 months) non-malignant, non-infectious lymphadenopathy or splenomegaly of both
  - Elevated CD3+TCR$\alpha\beta$+CD4-CD8-DN T-cells (>1.5% or total lymphocytes or >2.5% of CD3+ T-cells) with normal or elevated lymphocytes
- Accessory diagnostic criteria
  - Primary
    - Defective lymphocyte apoptosis
    - Germline or somatic pathogenic mutations in FAS, FASL or CASP10
  - Secondary
    - Elevated levels of FASL or IL-10 or Vit B12
    - Typical immunohistological findings
    - Autoimmune cytopenias and IgG levels
    - Family history

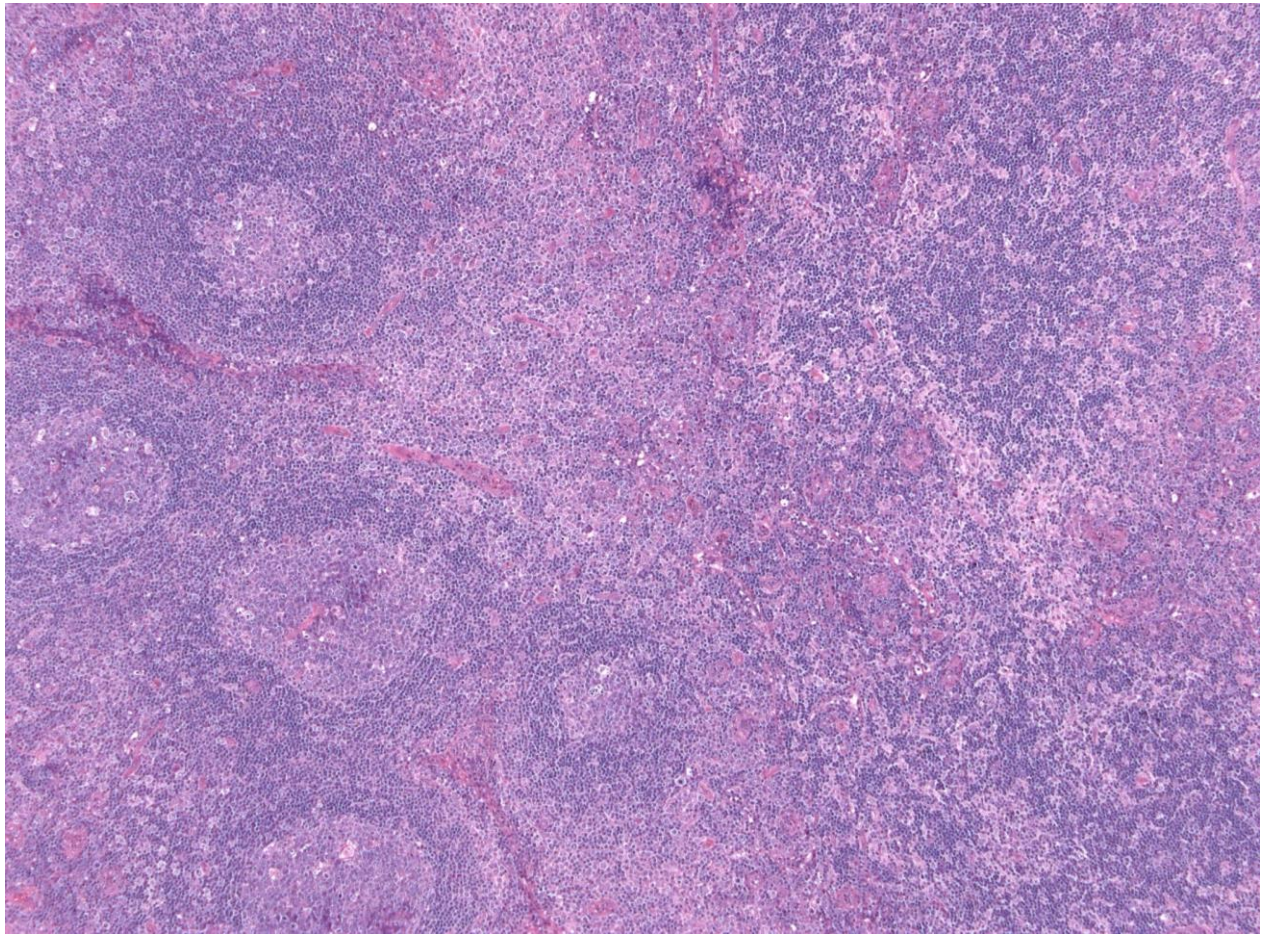
Oliveira et al, BLOOD 2010

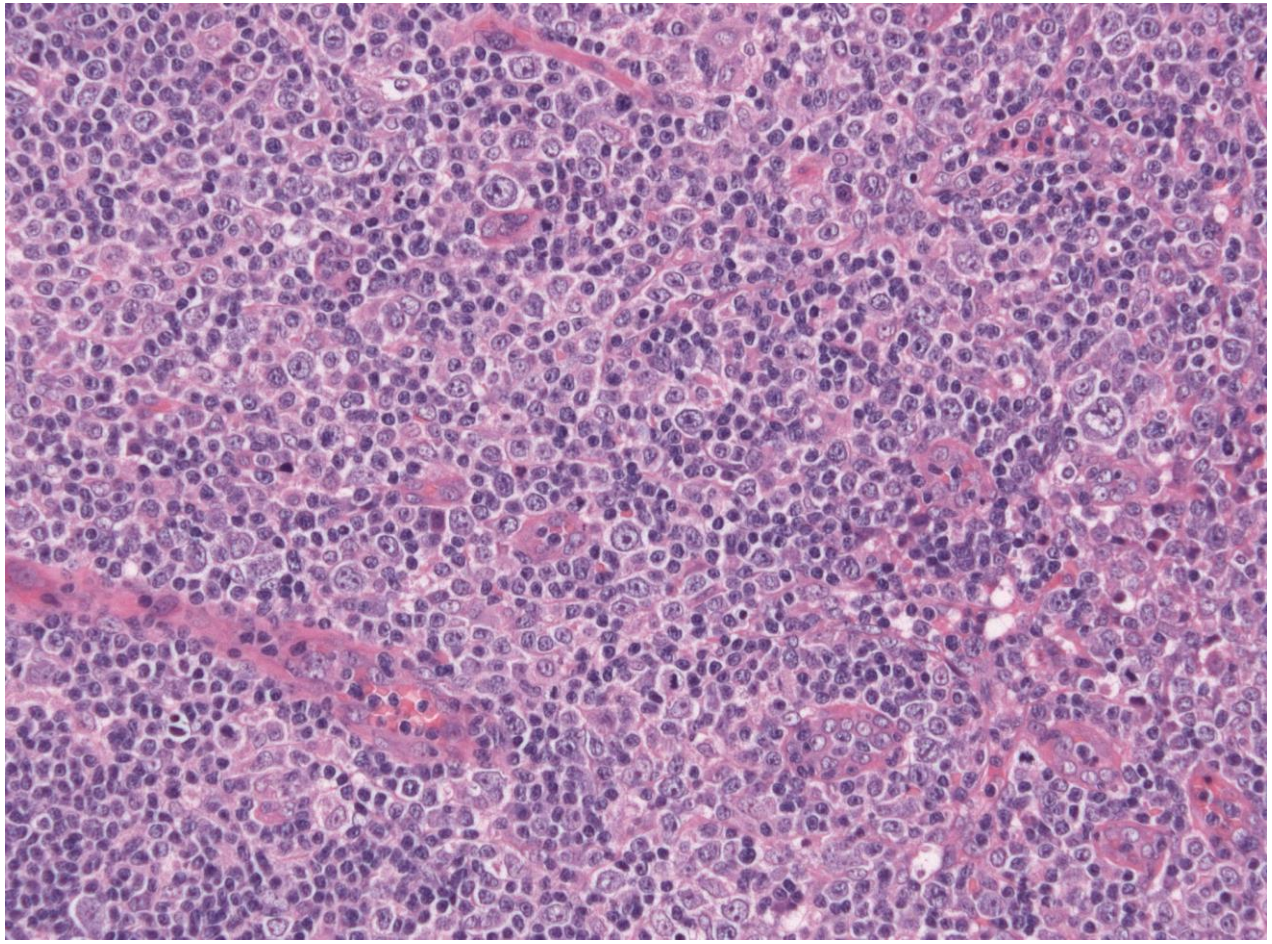
Interfollicular hyperplasia

- 16-year-old young male
- Partially preserved LN architecture



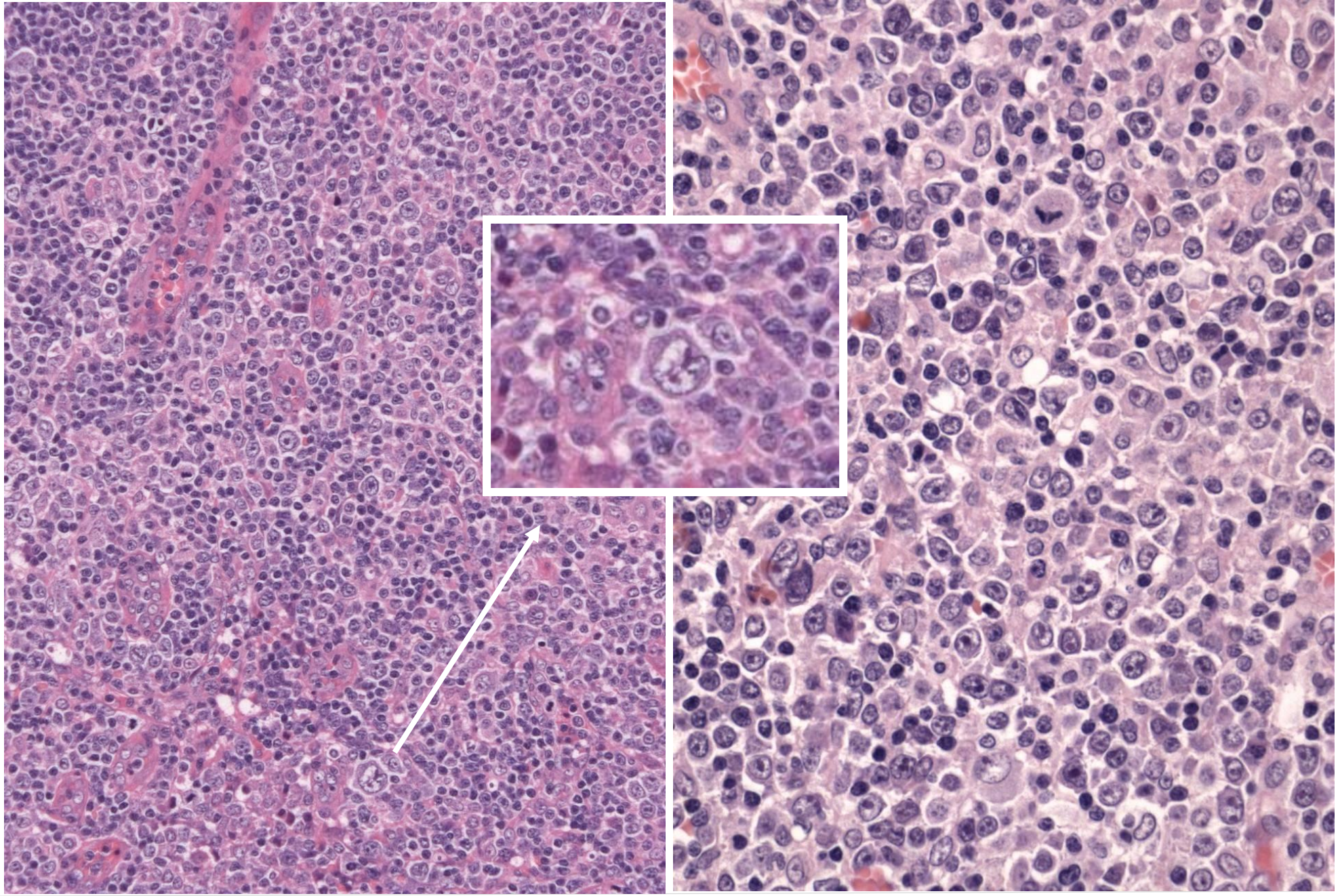
Interfollicular hyperplasia

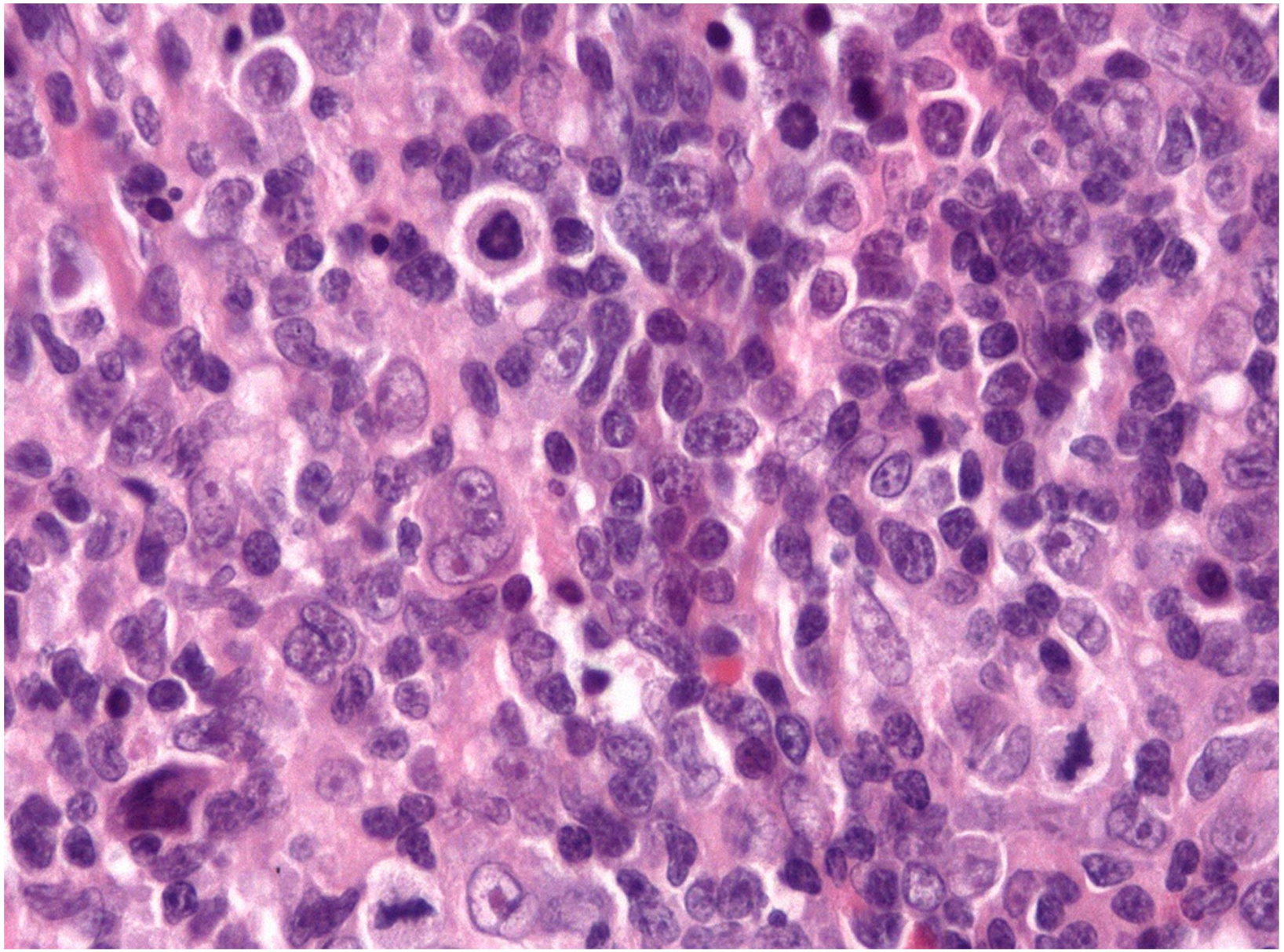


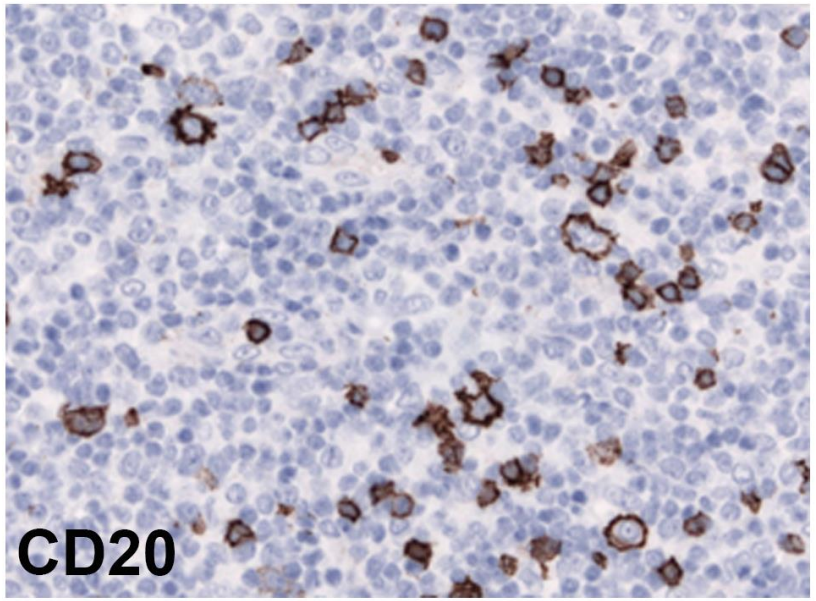


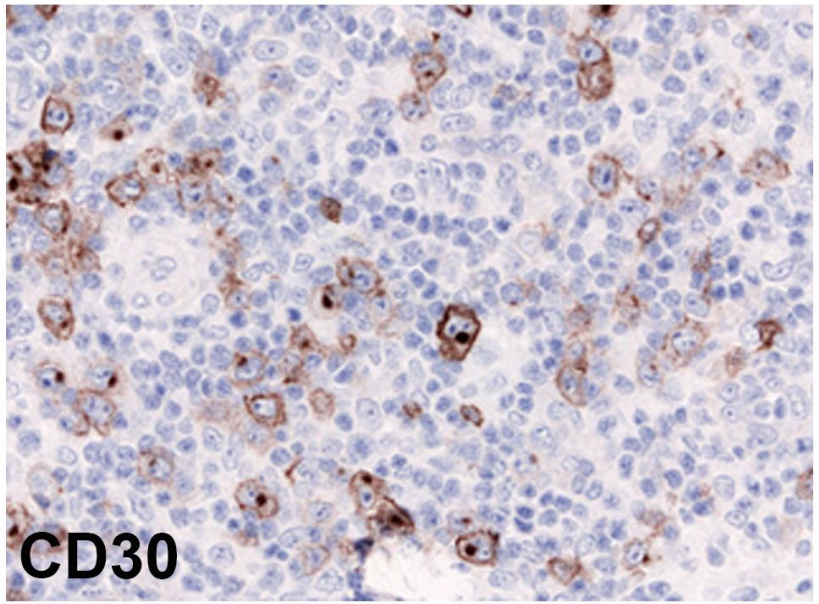
- Polymorphic infiltrate
- Many large immunoblast

- DD: SLE, autoimmune diseases, drugs, viral infection.
- DLBCL, CHL

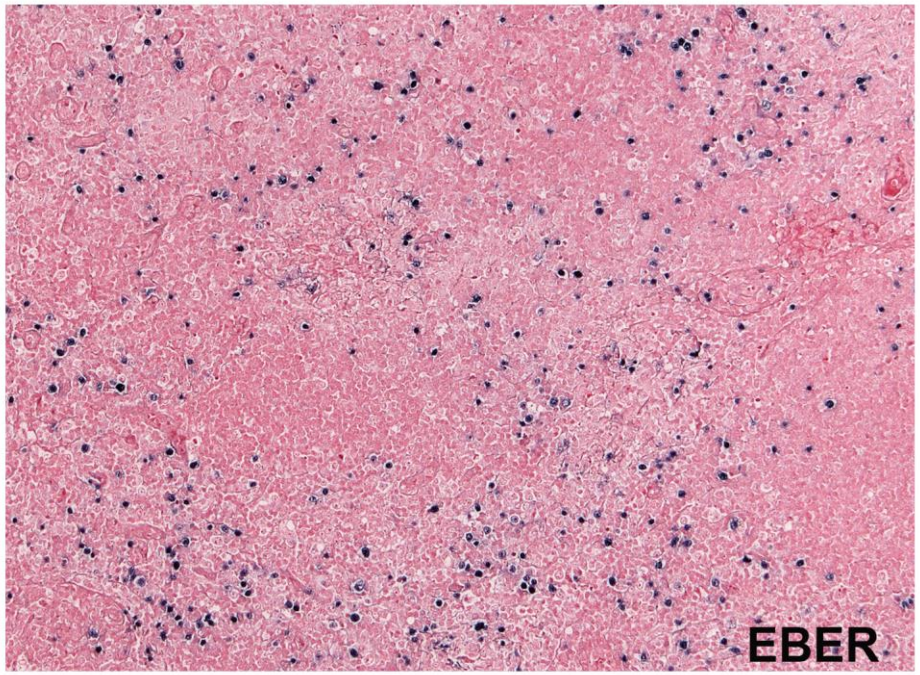


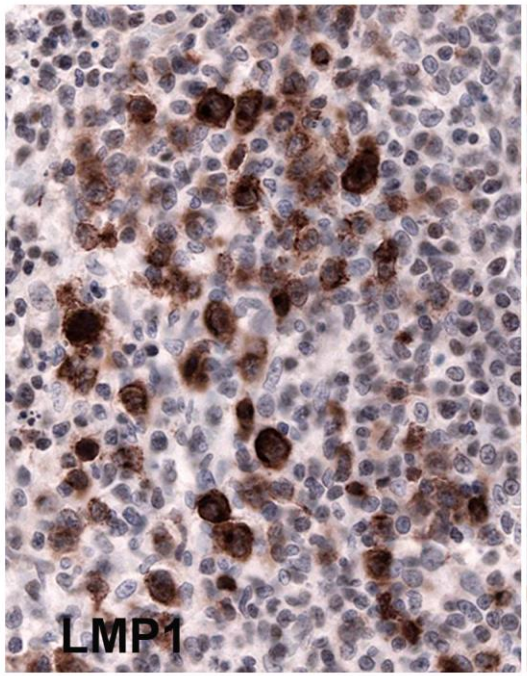


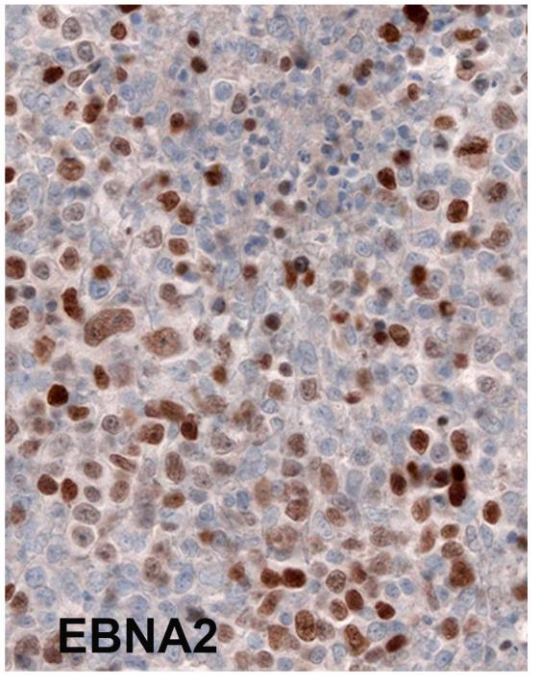

CD20


CD30

Infectious mononucleosis



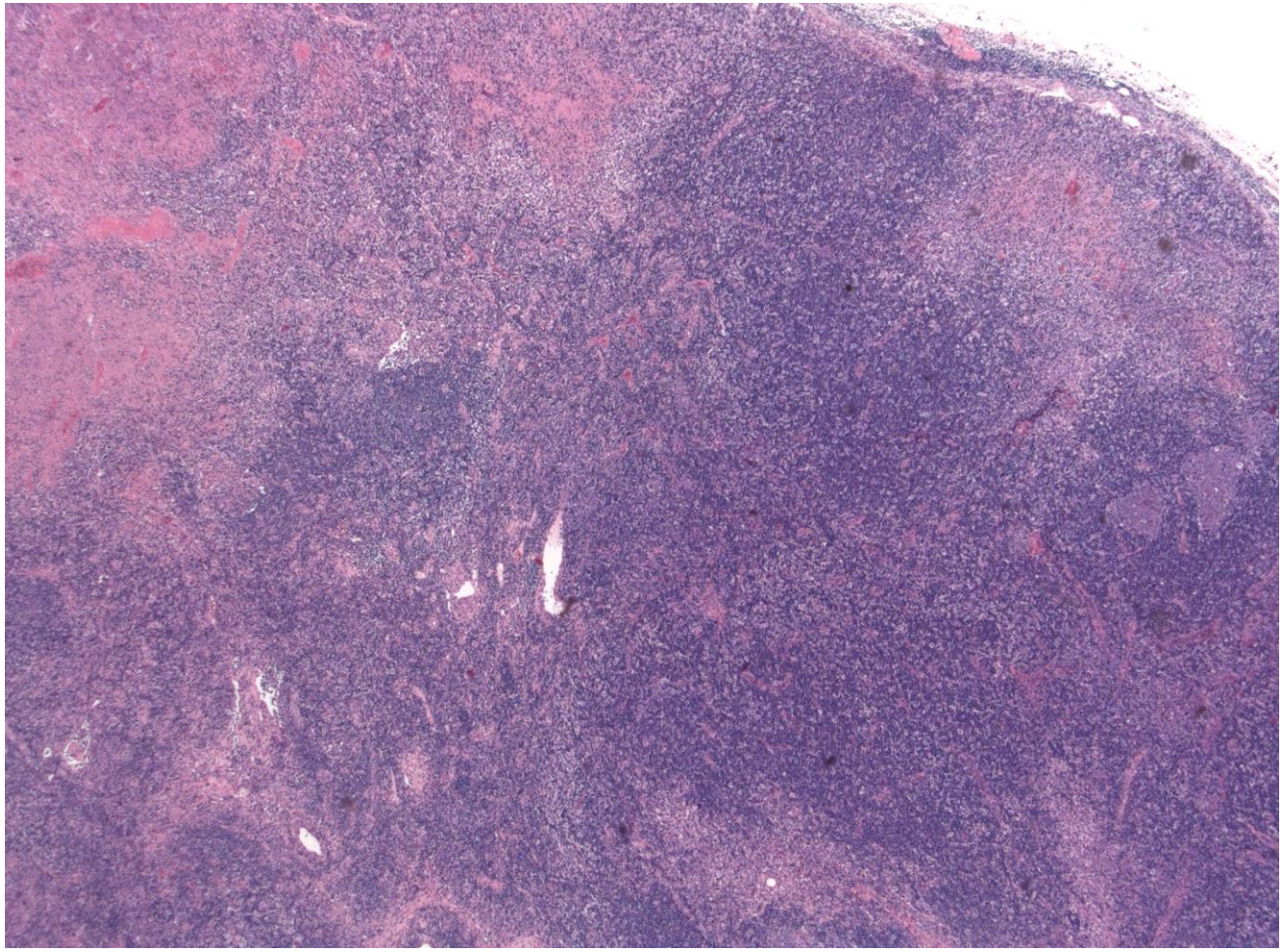




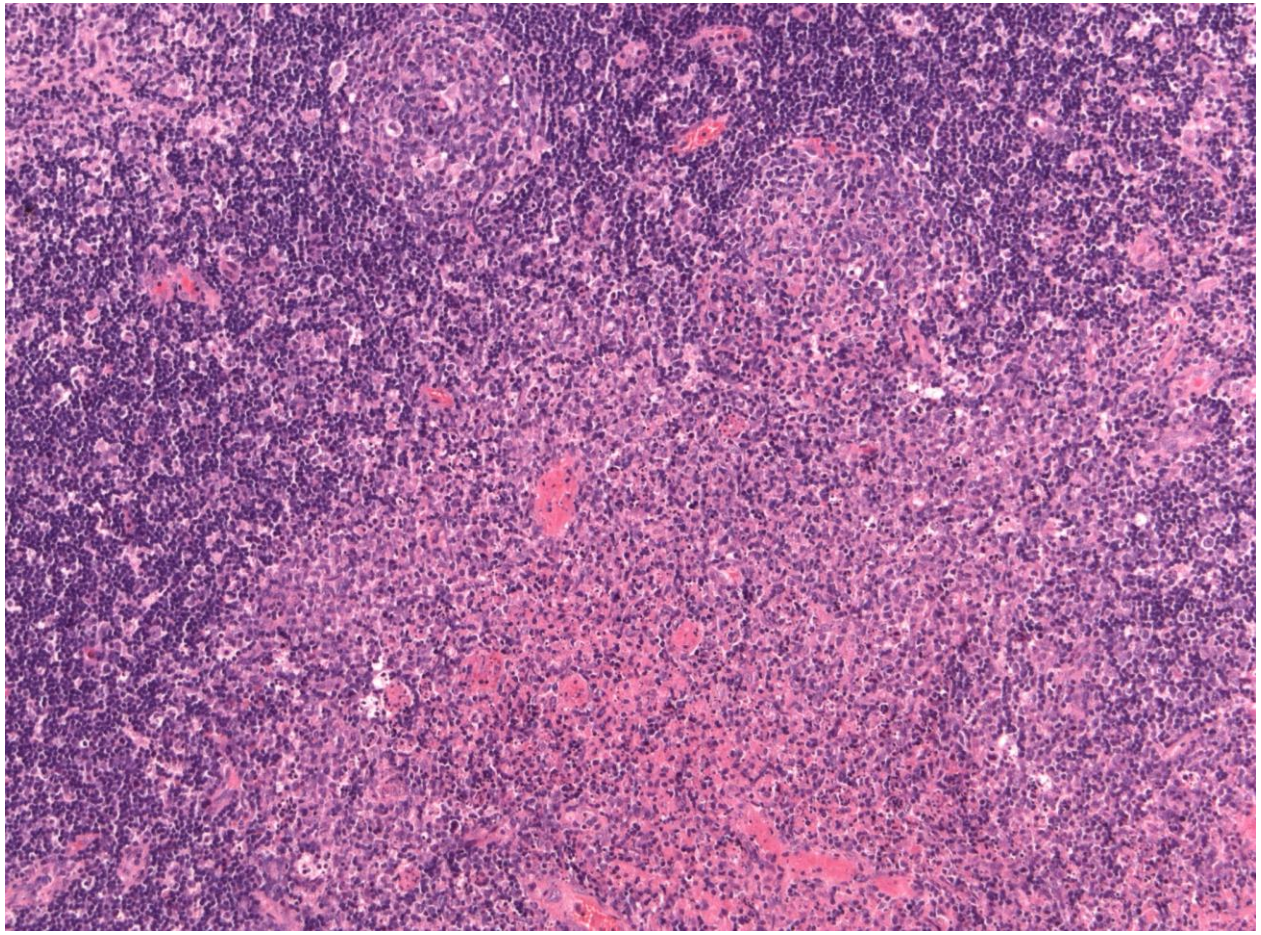
- Usually young adults, tonsils and cervical nodes
- EBV reactivation may occur at any age
- Diffuse interfollicular hyperplasia with many blasts of different size and maturation status, polytypic IG in plasmablasts and plasma cells
- Frequently RS-like cells, CD30+, CD20+/-, CD15-, EBV latency type III
- Many activated cytotoxic T-cells, both B- and T-cell clonality may be present

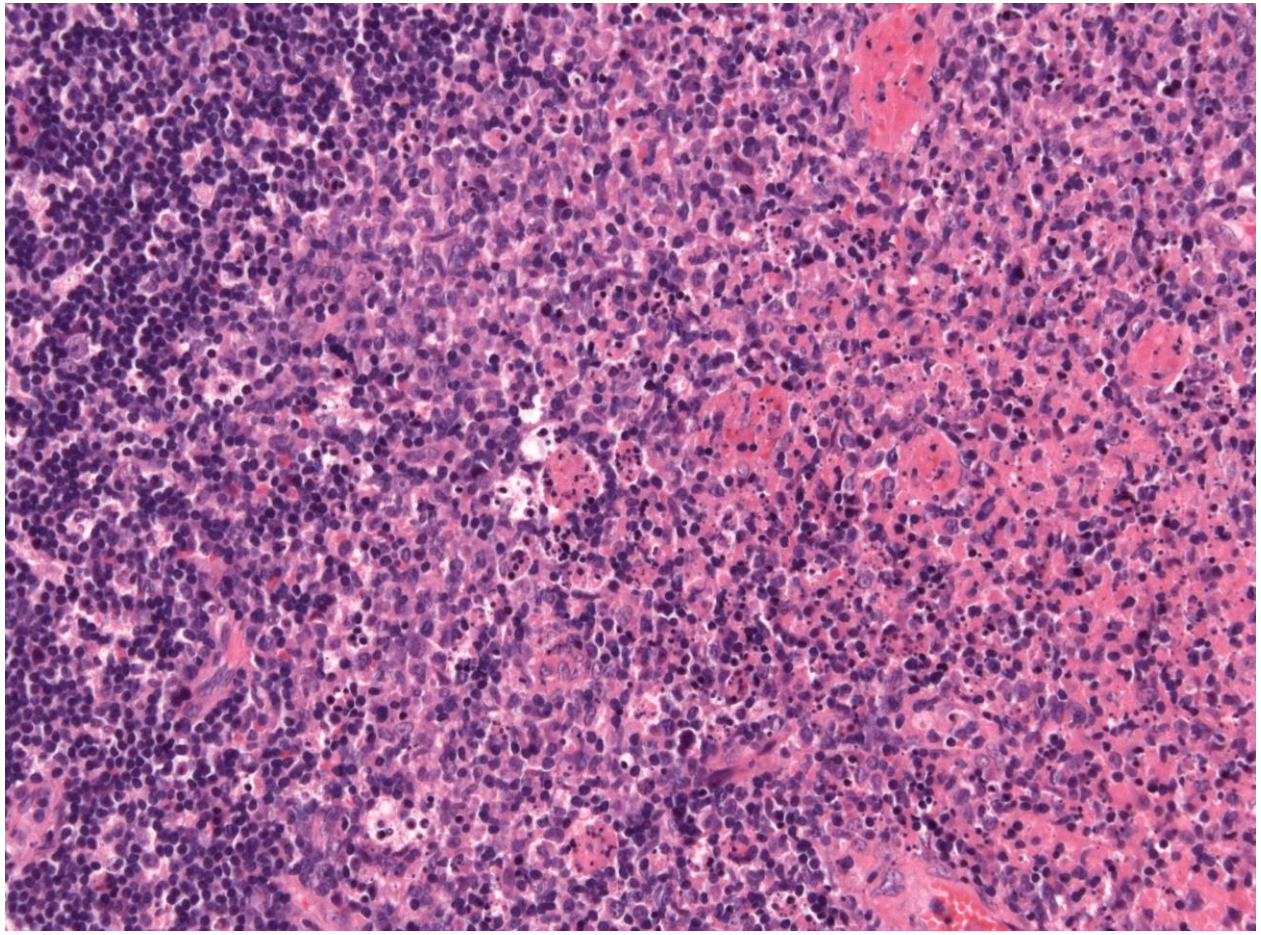
Necrotizing lymphadenitis

- 18 year-old-female with isolated cervical lymphadenopathy, fever



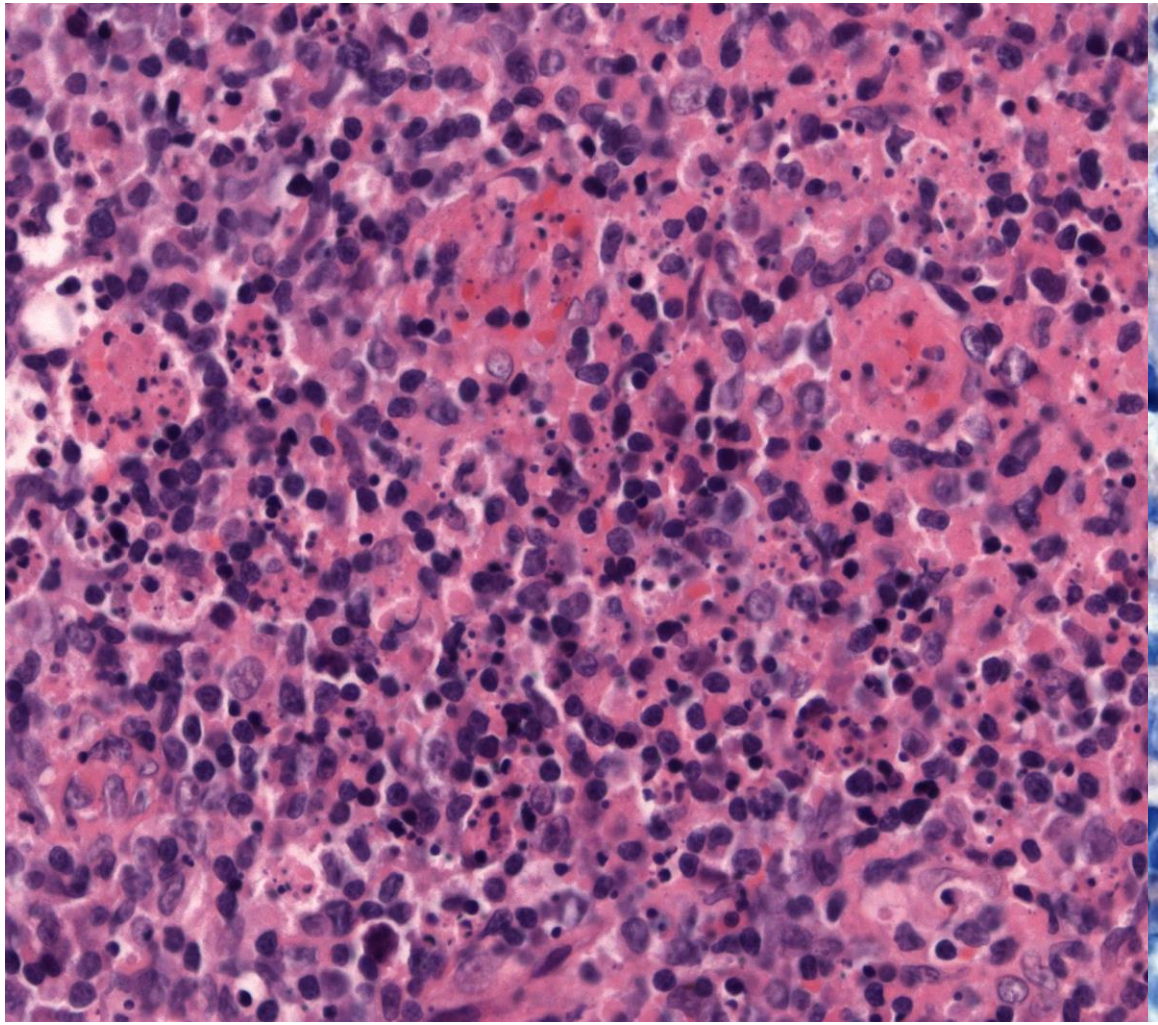
Paracortical necrosis

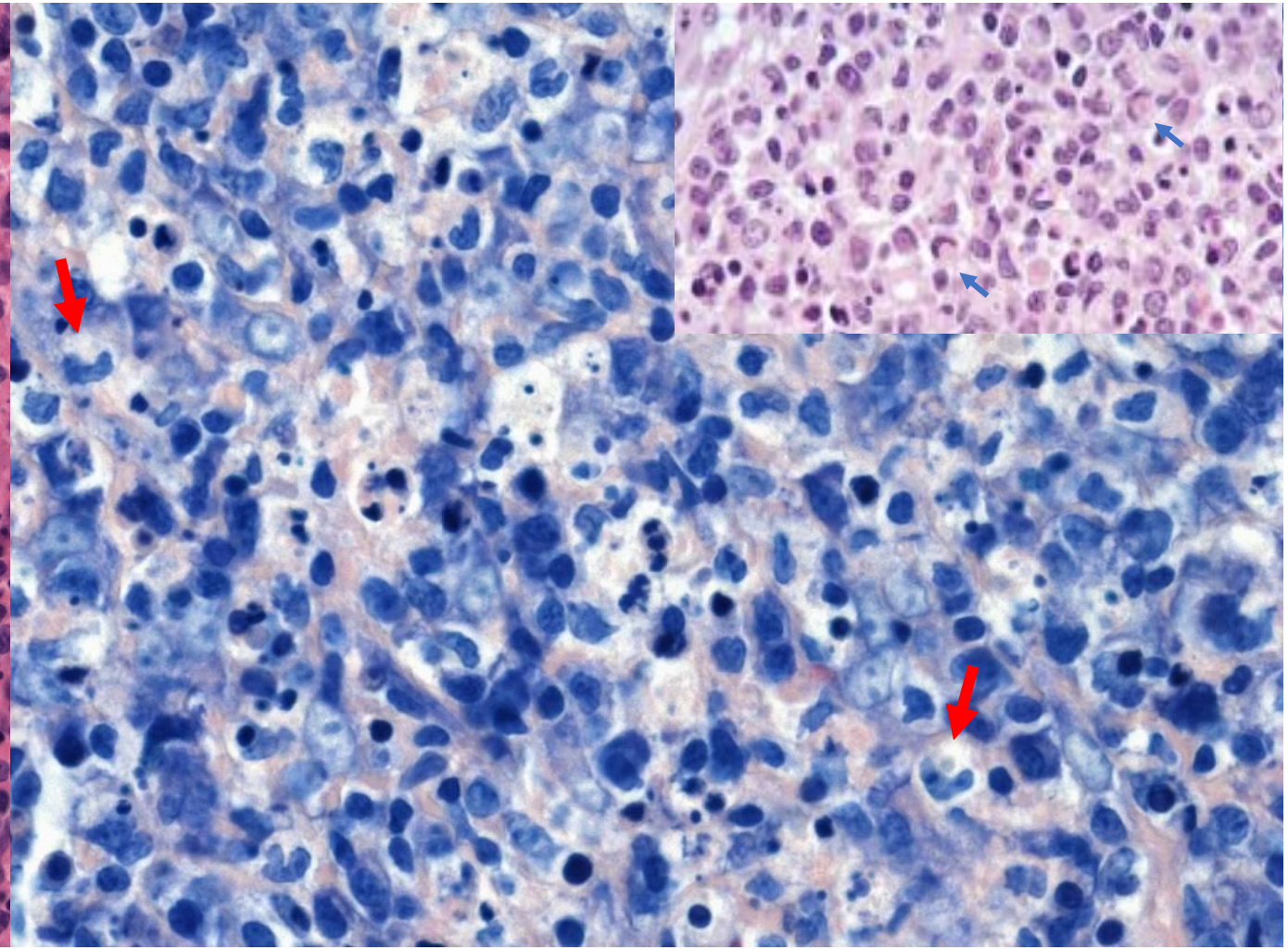




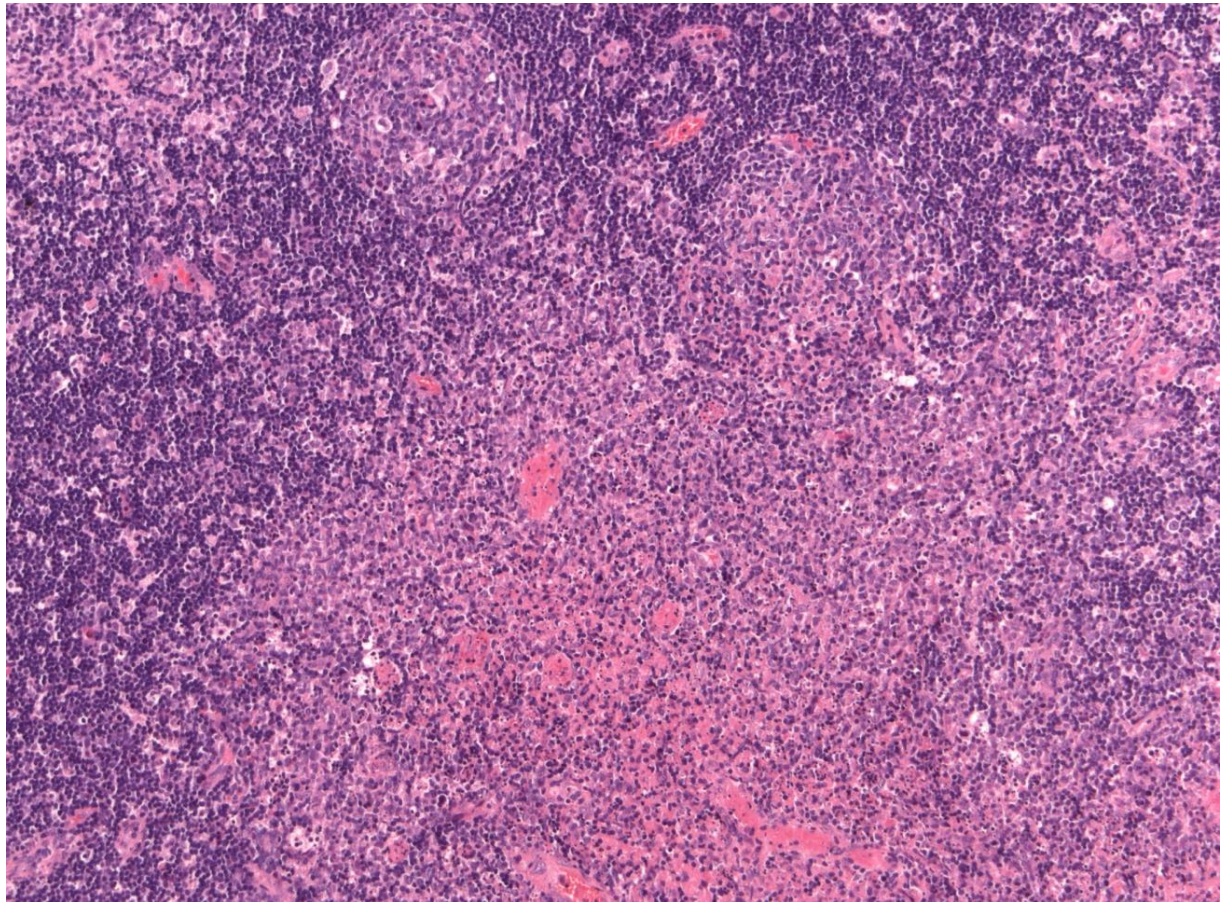
Follicular hyperplasia
Necrosis (Karyorrhexis with abundant histiocytes and absence of neutrophils
Necrosis surrounded by Plasmocytic dendritic cells (PDC)

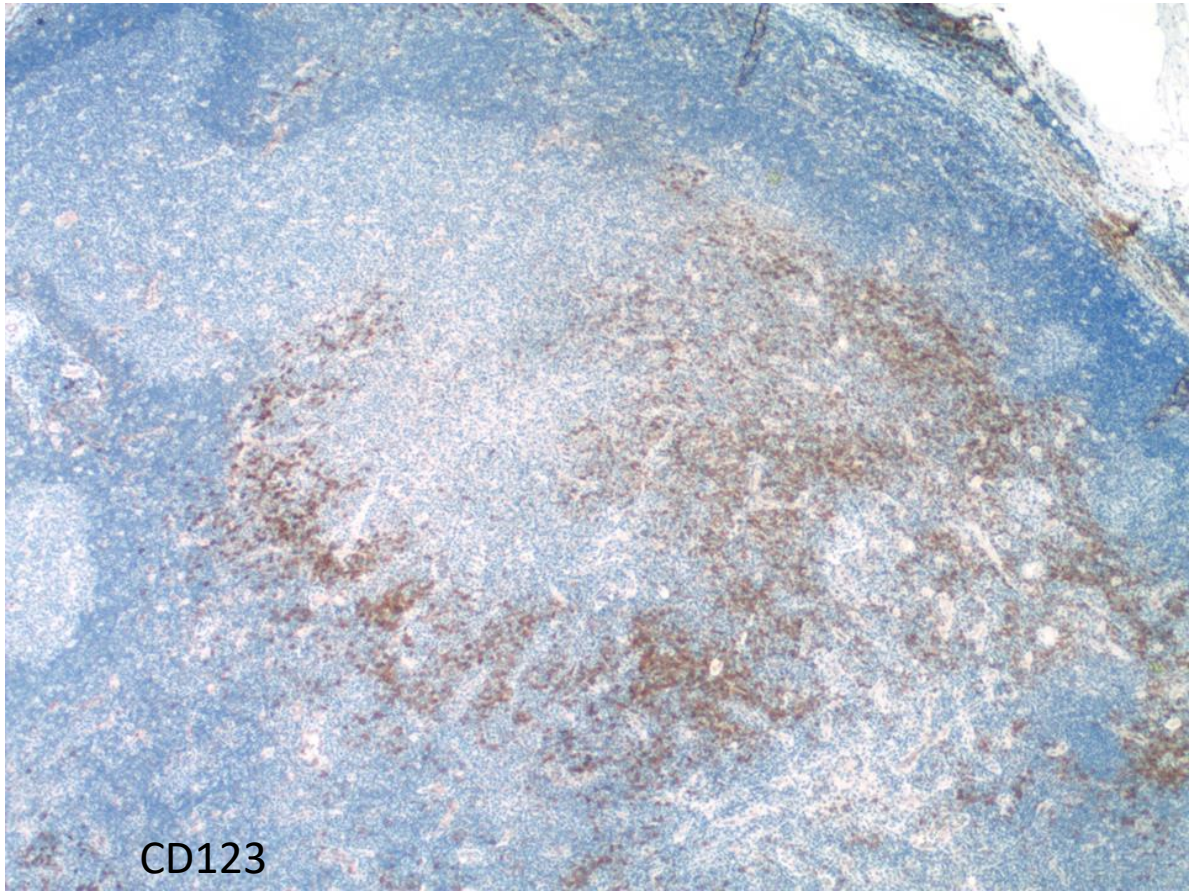
Histiocytic necrotizing lymphadenitis





Histiocytic necrotizing lymphadenitis





Kikuchi´s lymphadenitis

- Mostly partial involvement of node by diffuse proliferation of large cells and histiocytes with coagulative necrosis without granulocytes
- Crescent-shaped histiocytes, MPO+
- Paracortical clusters of plasmocytoid dendritic cells

Immunophenotype:

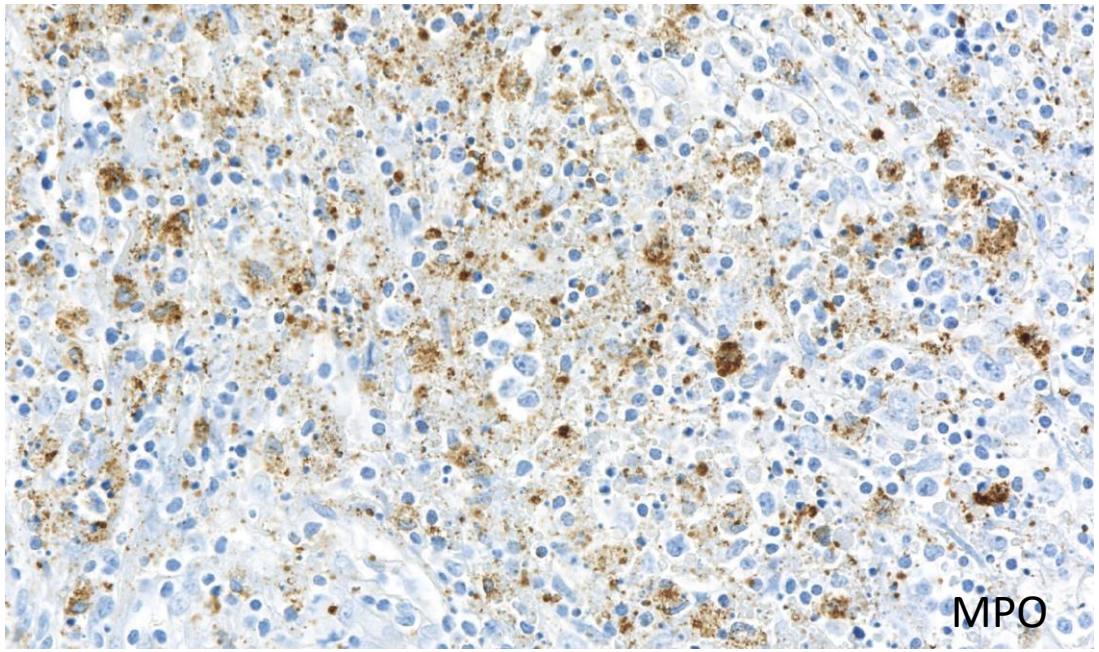
- Mixed B- and T-cells
- Plasmacytoid dendritic cells (CD123+)

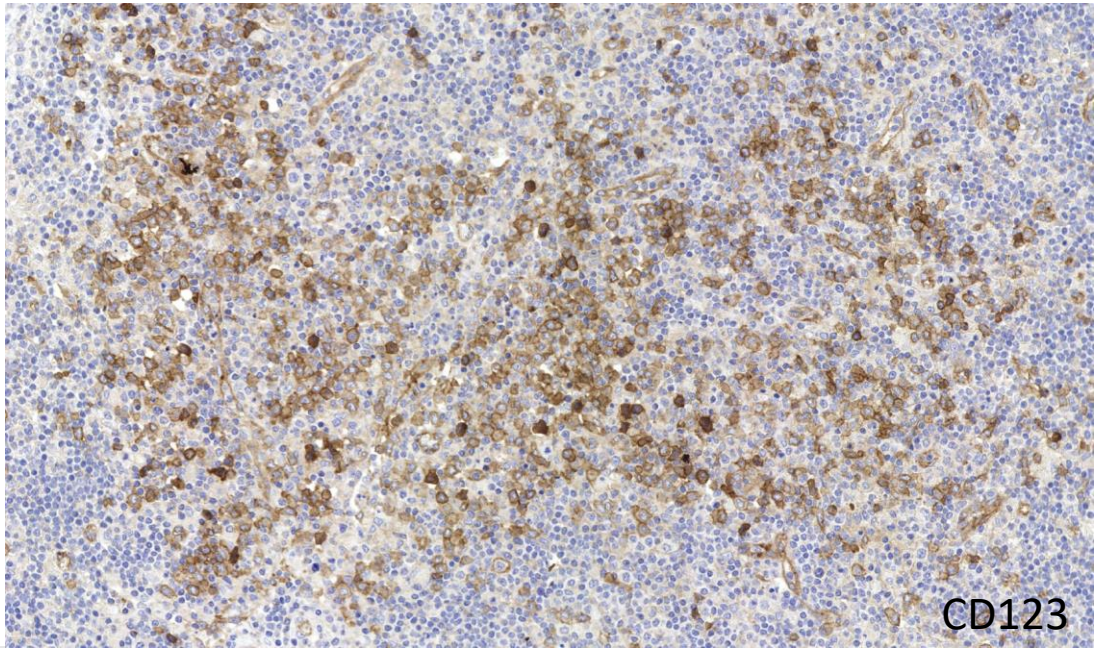
Differential Diagnosis:

- Partial involvement by large cell lymphoma, especially cytotoxic T-NHL

Clinical features:

- Mostly young females
- Usually isolated cervical node, generalized LAP rare
- Fever common, otherwise good health

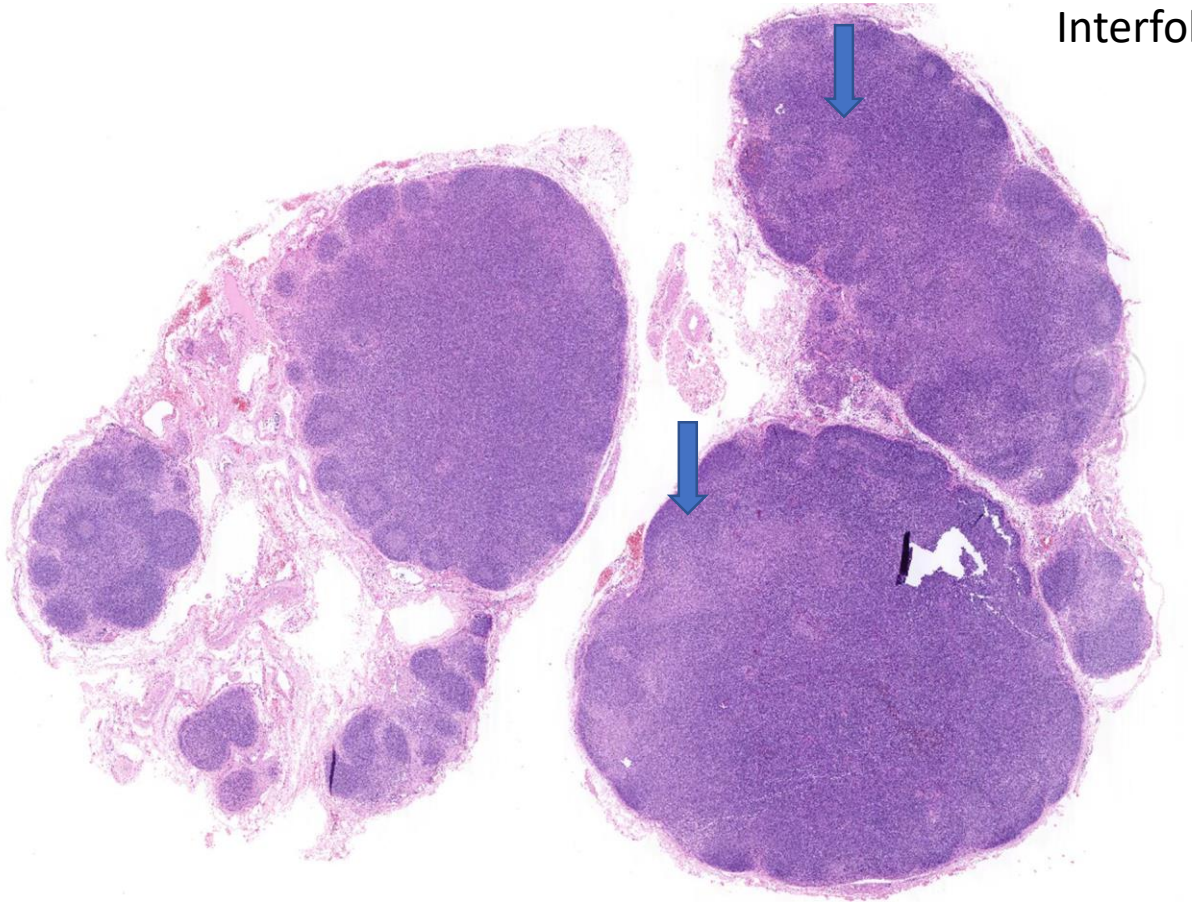




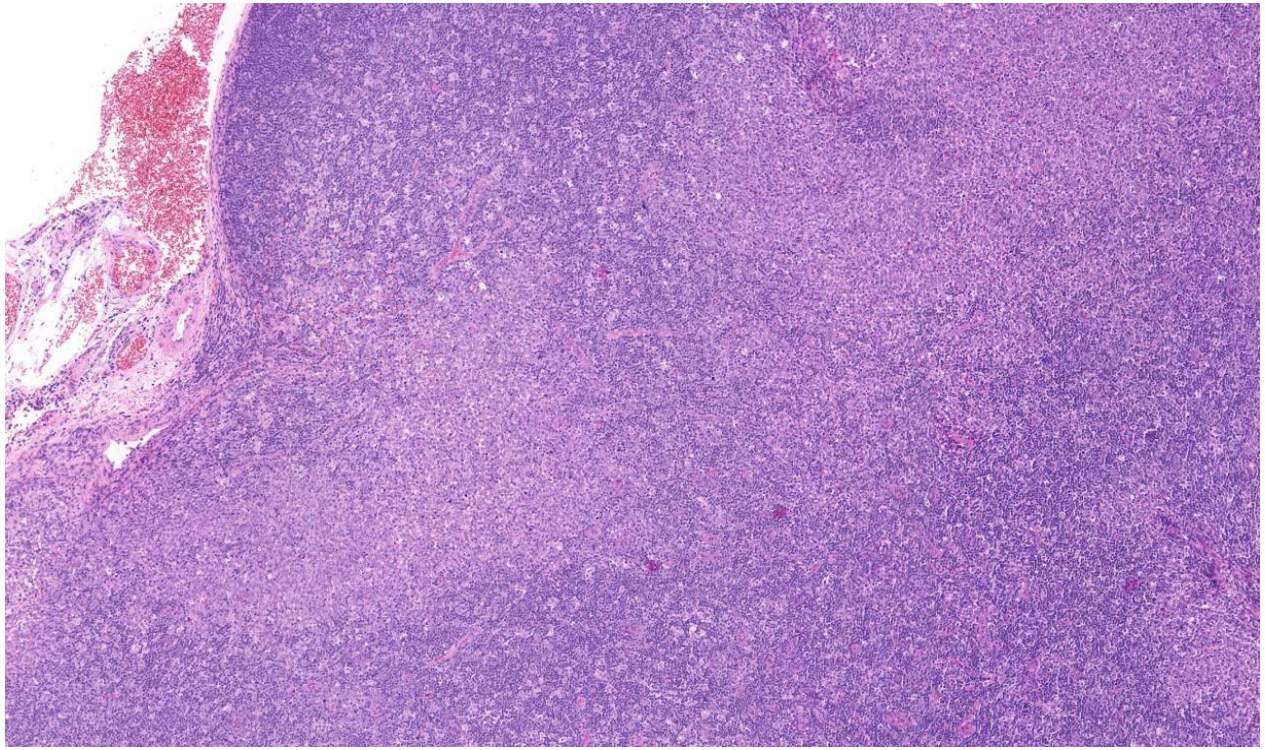
Pathological features

- Preserved or partially preserved architecture with follicular hyperplasia
- Three stages are recognized:
  - Proliferative stage: expanded paracortex with sheets of histiocytes and plamocytoid dendritic cells, immunoblasts admixed with small lymphocytes
  - Necrotizing stage: areas of necrosis with abundant karryorrhetic nuclear debris and a large accummulation of histiocytes at the edge of teh necrosis. Frequent crescentic histocytes. Neutrophils and eosinophils are absent (requiered)
  - Xantomatous stage: predominance of foamy histiocytes
- Immunophenotype: histiocytes (CD68, CD4, MPO), PDC (CD123), lymphocytes (CD8 mainly).
- DD: Non-Hodgkin lymphoma or autoimmune lymphadenitis (Systemic Lupus)

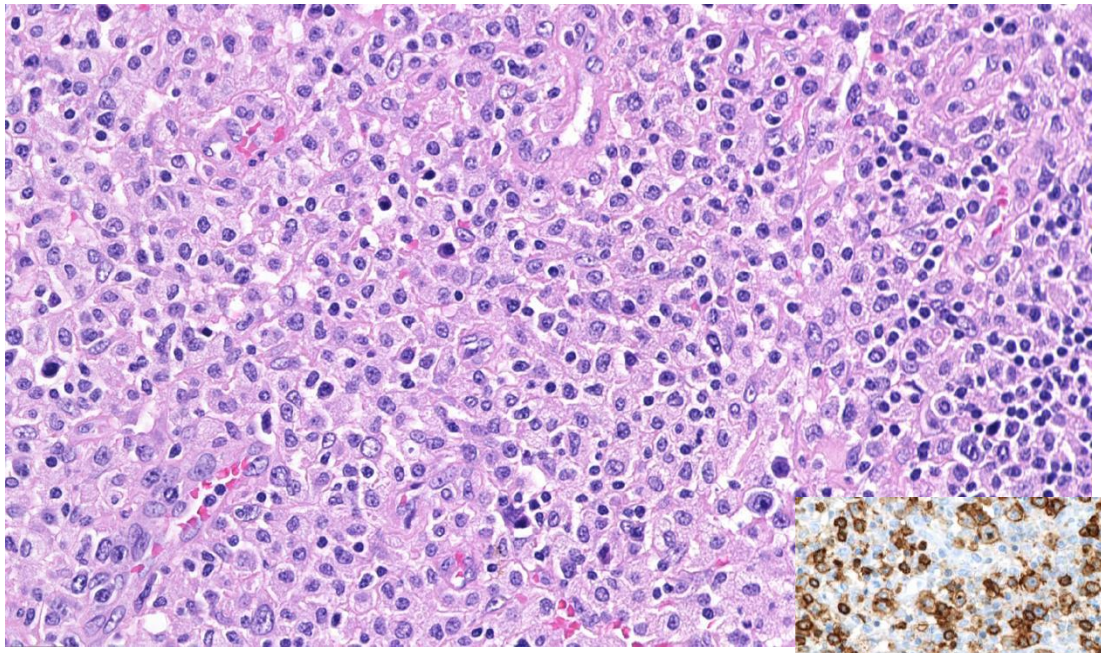
Eearly proliferative stage

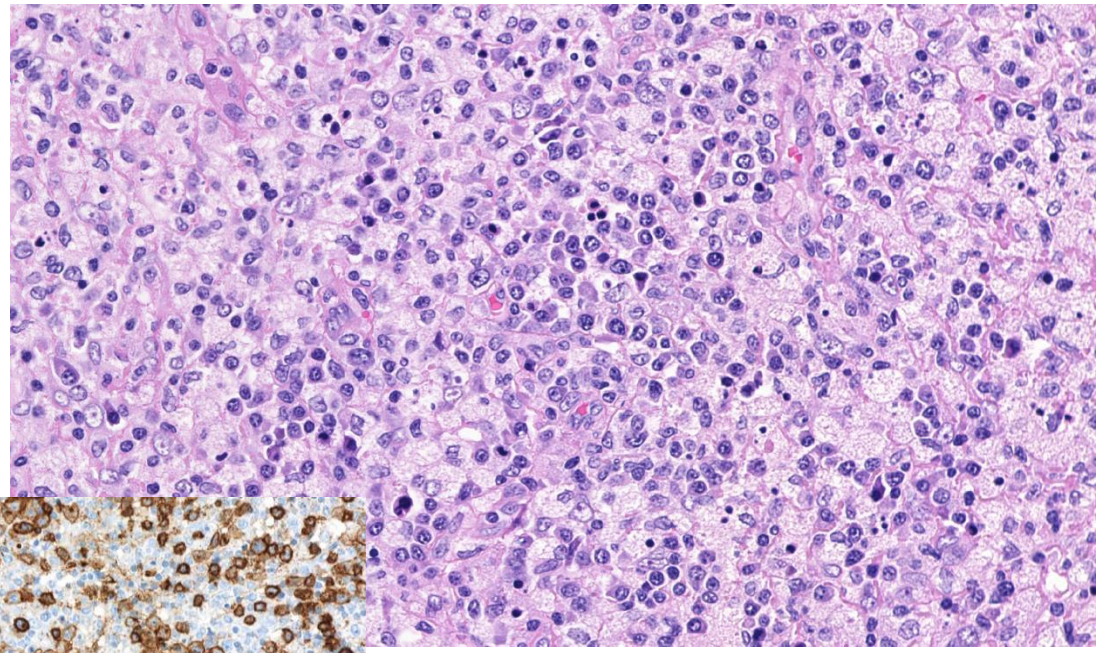


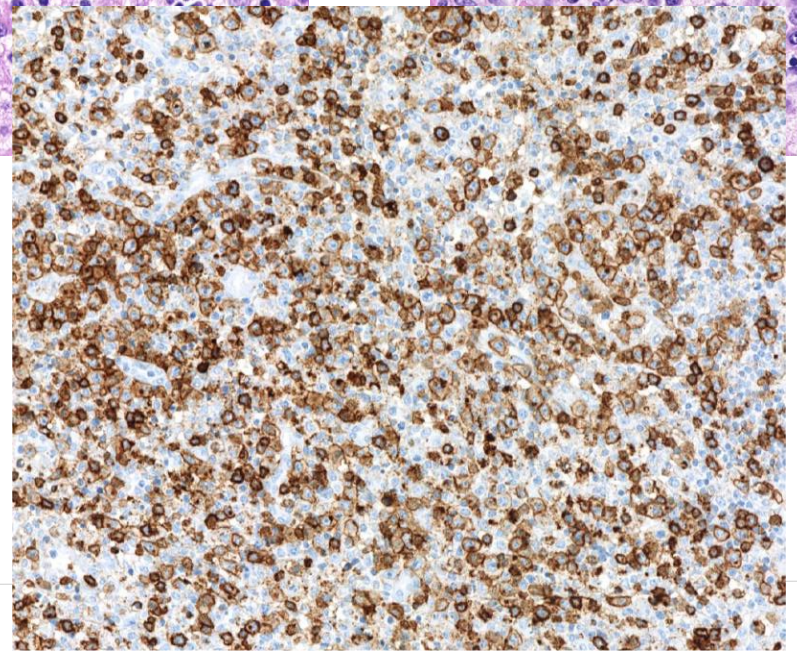
Lymph node with preserved architecture, follicular hyperplasia and Interfollicular lighter areas



Proliferative areas





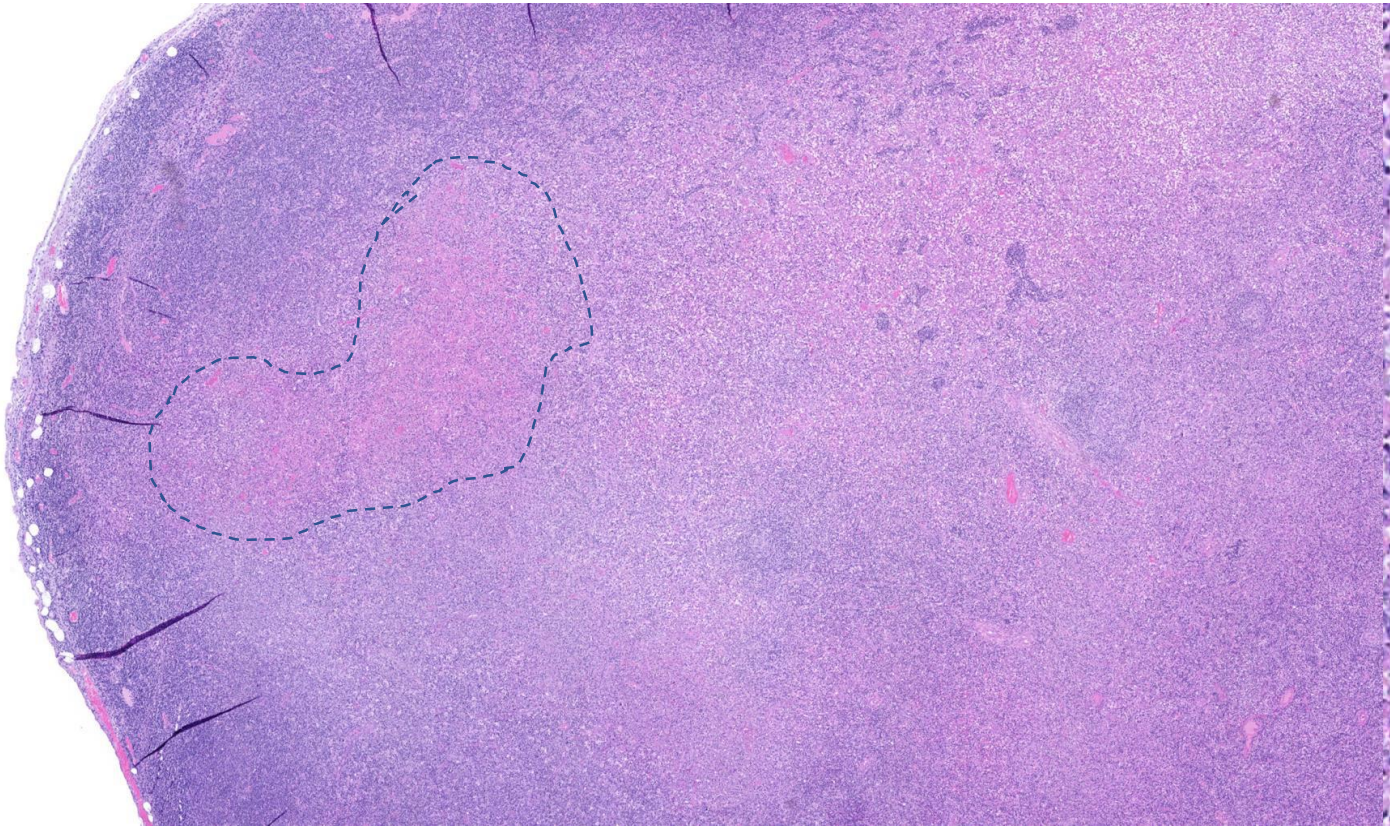


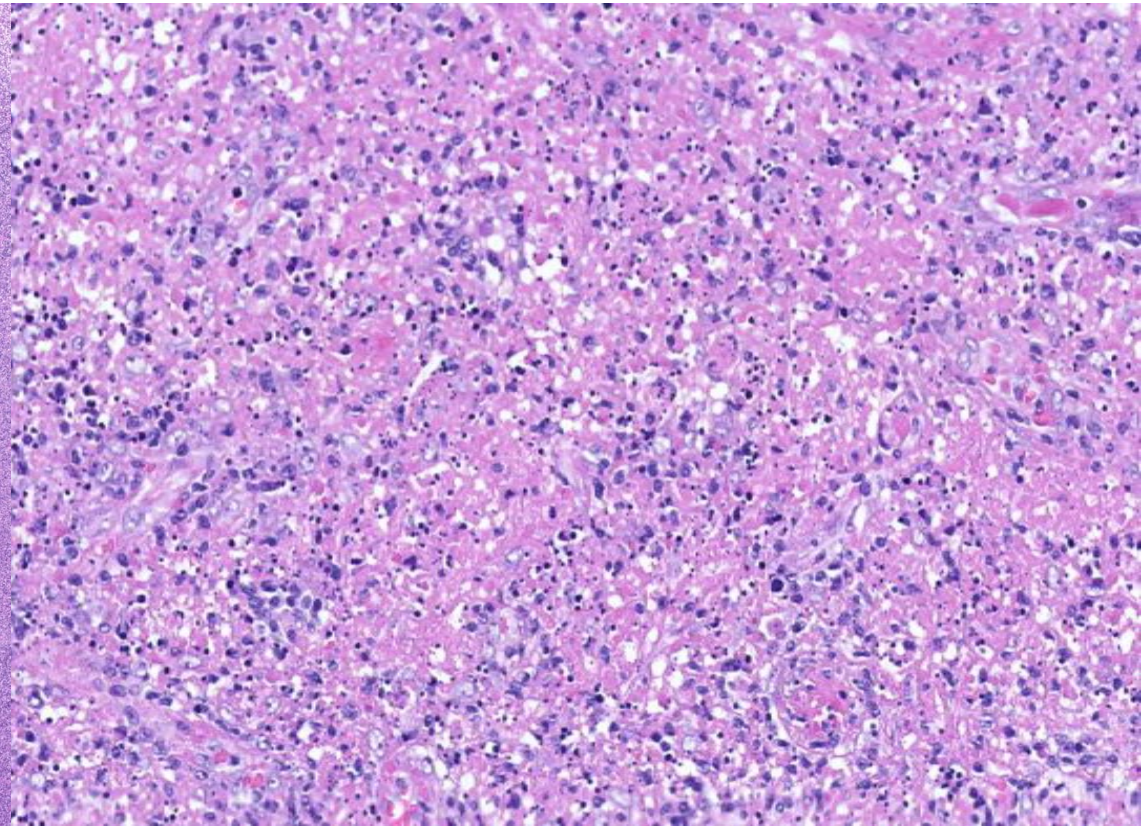
In the lighter areas a mixture of different cells, especially of medium sized cells, intermixed with large immunoblast raising the diagnosis of DLBCL

Atypical large cells, CD8+

Be careful! Not to diagnose NHL

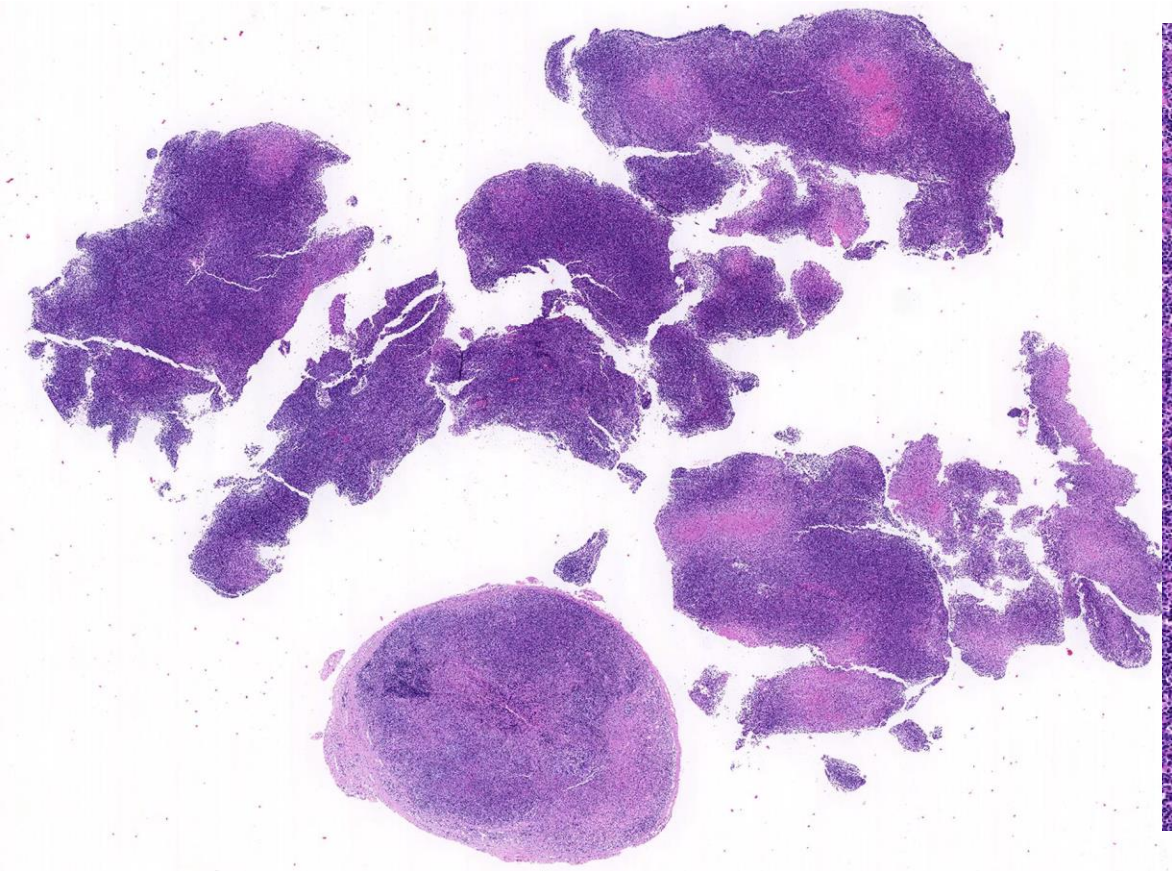
Eearly necrotizing stage

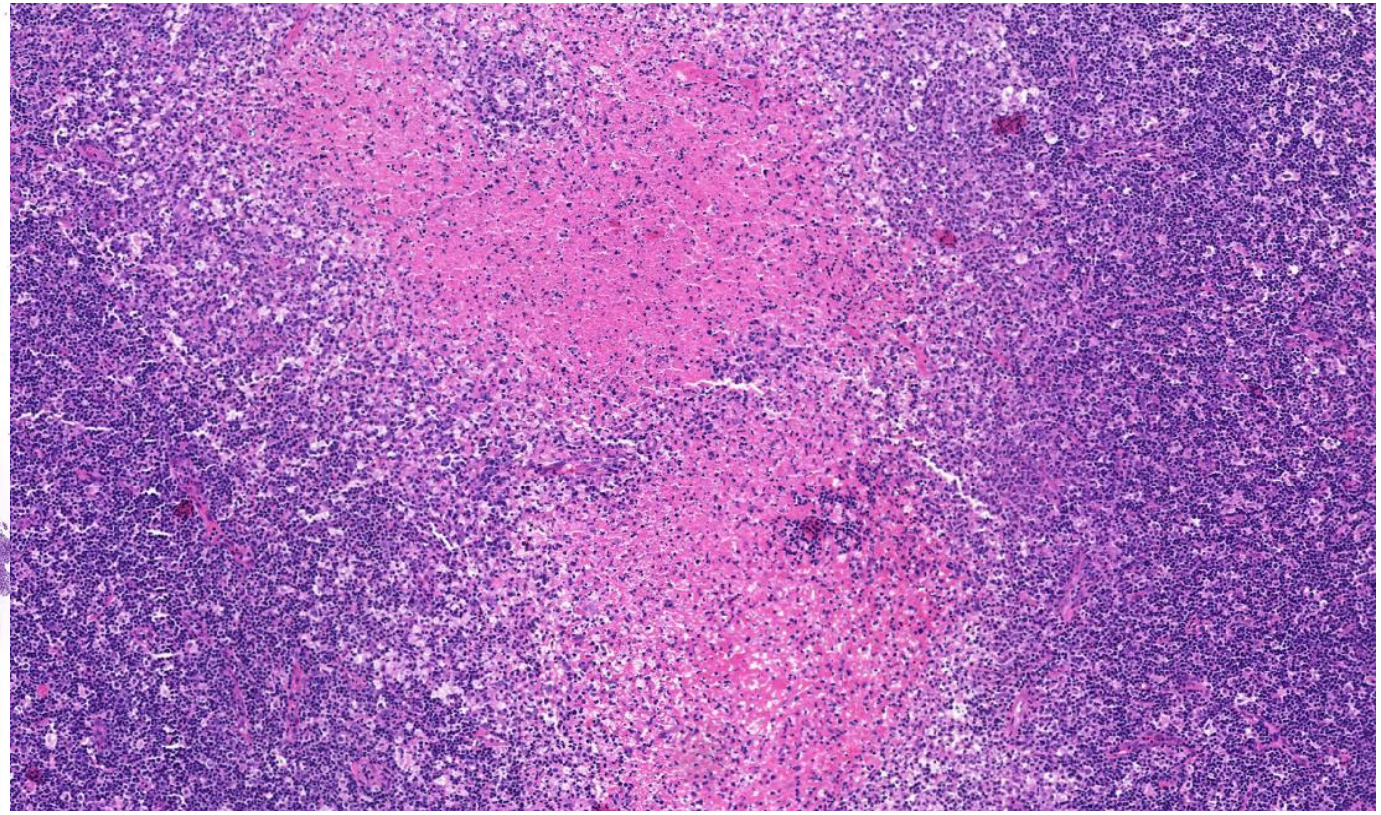




Advanced necrotizing stage

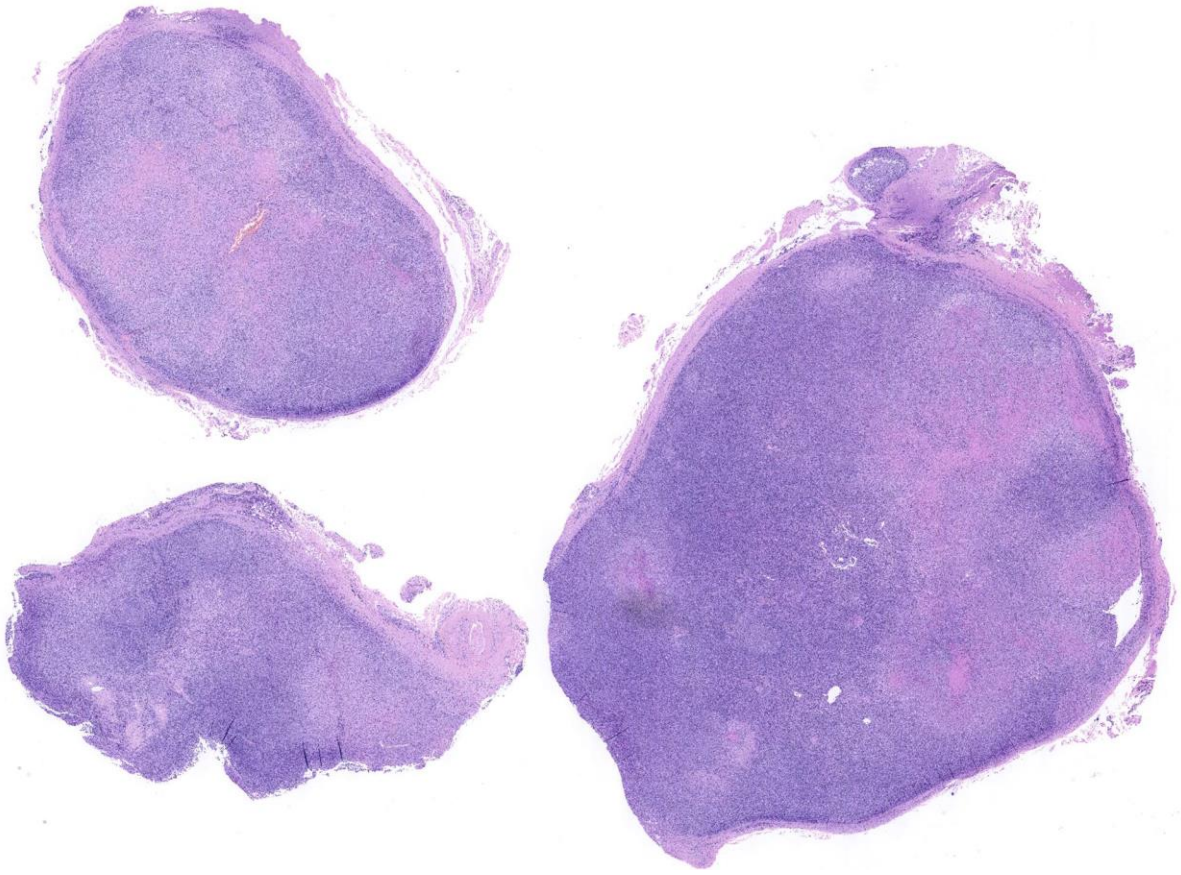
Seen in most cases and is characterized by patchy areas of necrosis within the paracortex

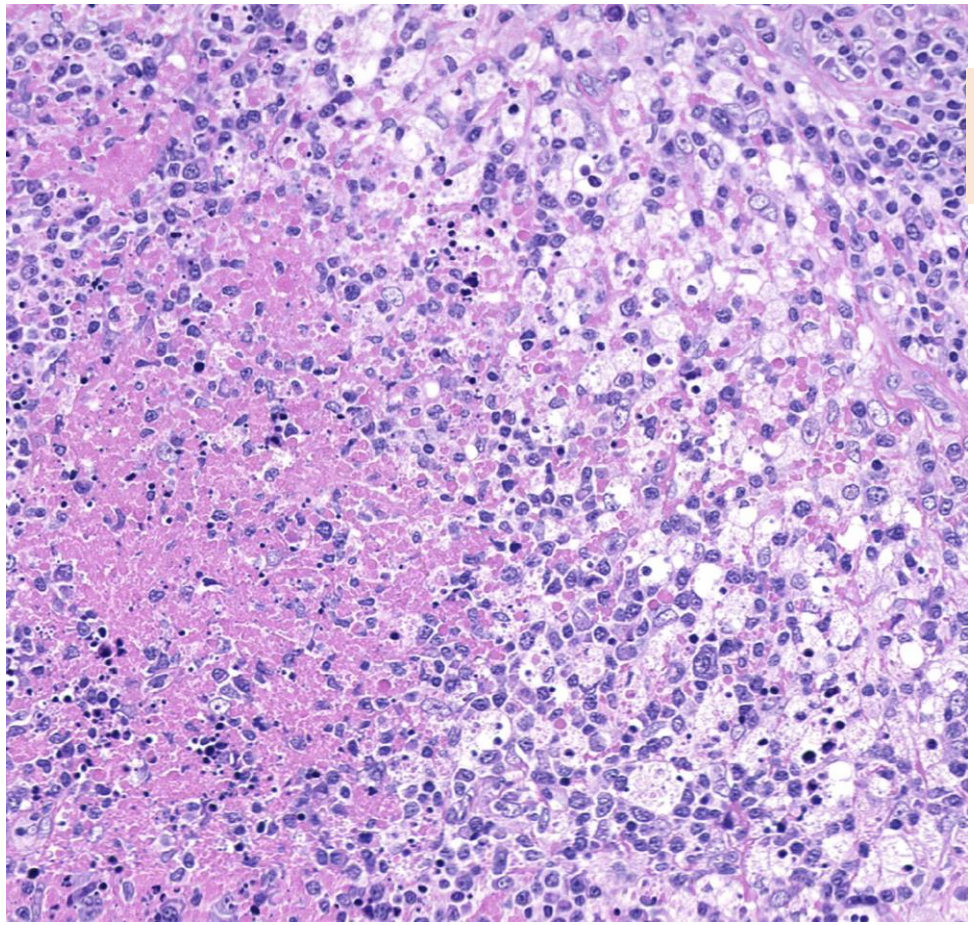




Xantomathous stage

Is the least common and most likely represents the healing phase of the entity

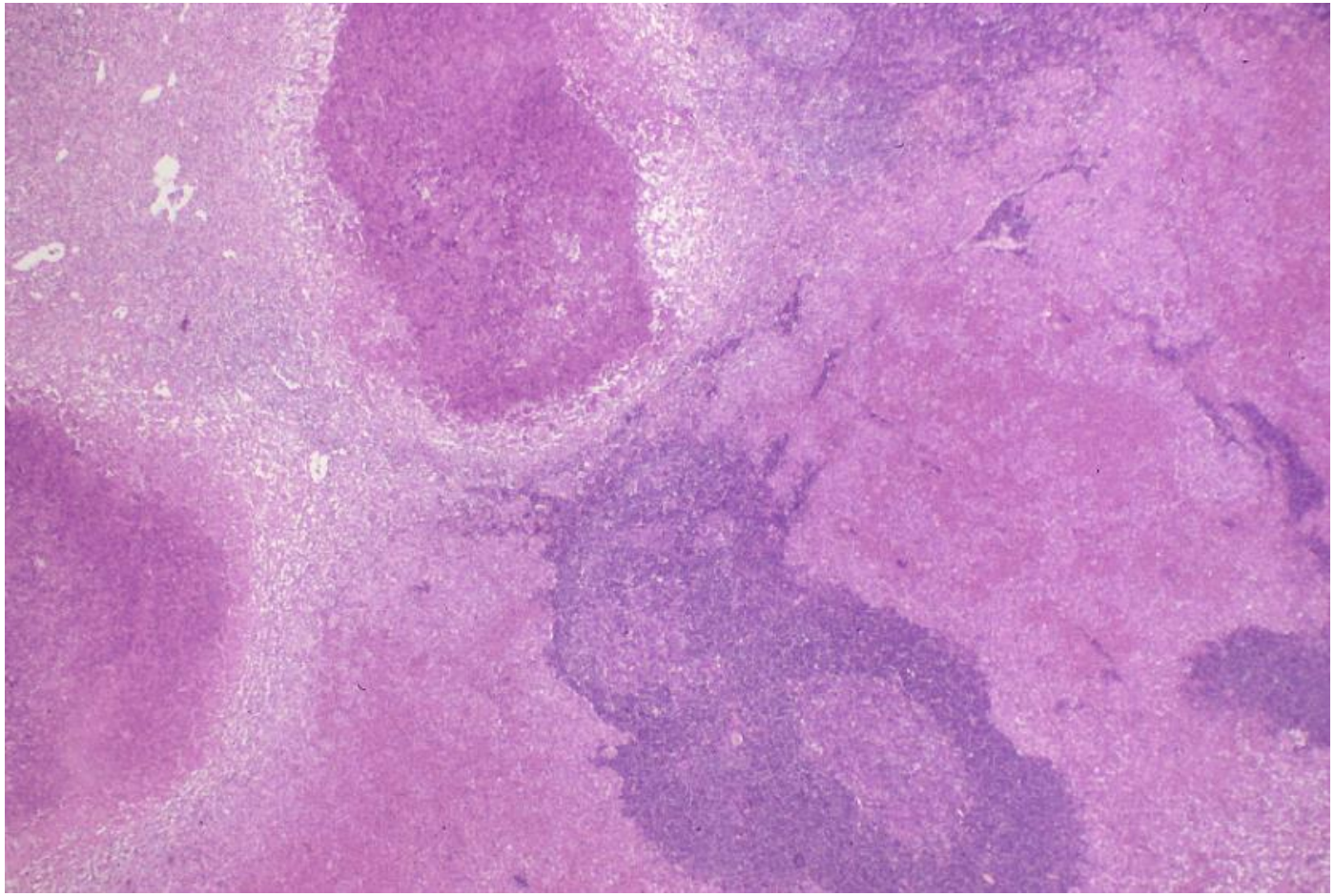




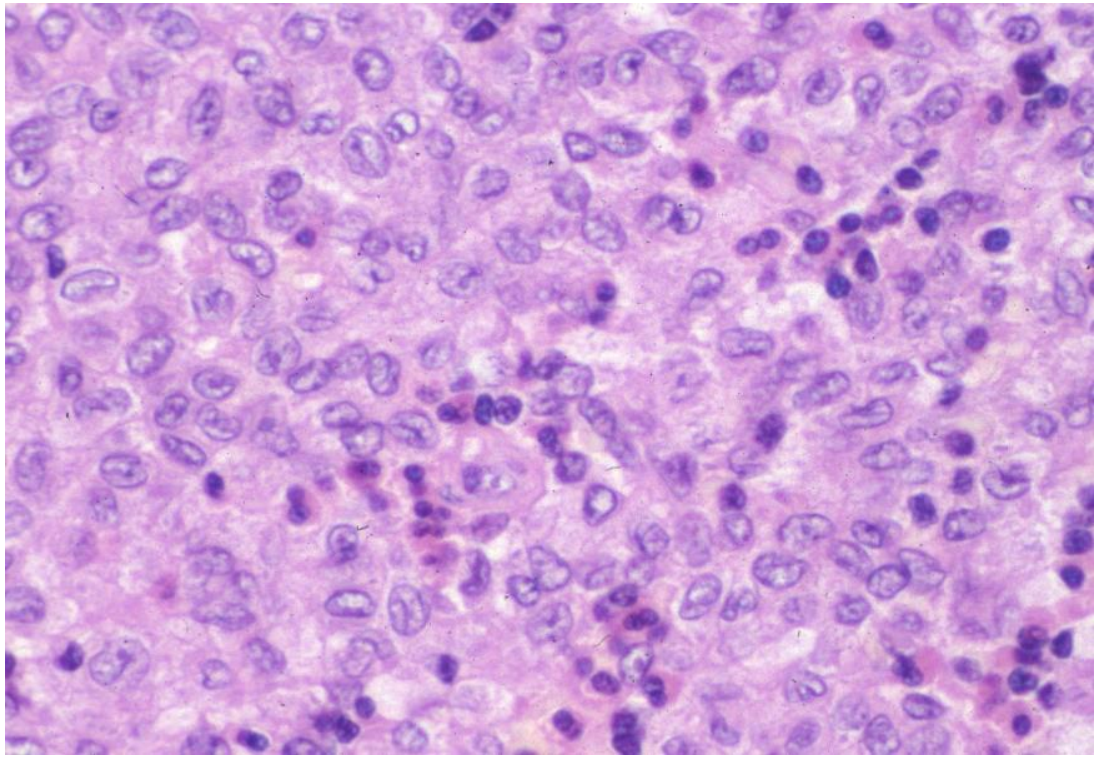
Foamy macrophages

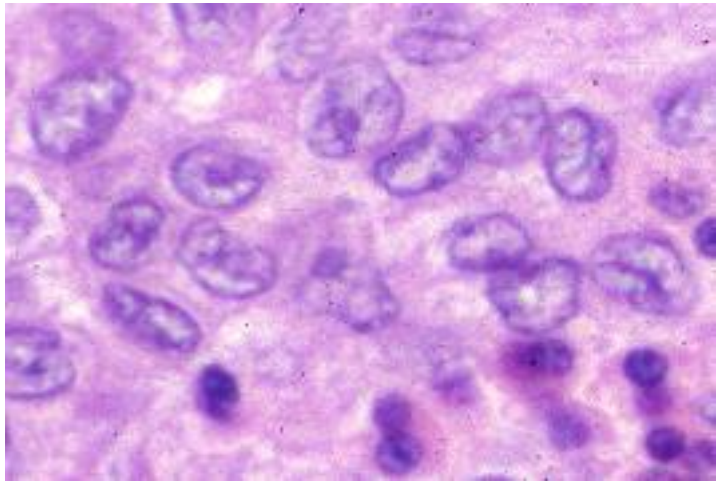
Necrotizing lymphadenitis?

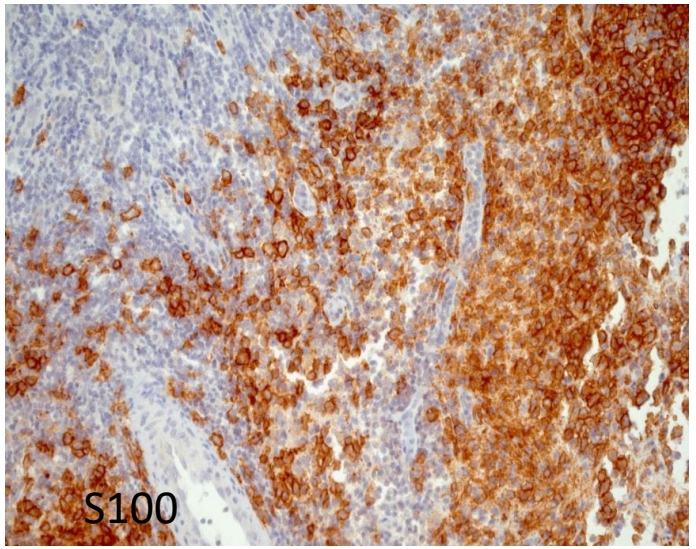
- 3 year-old female with cervical lymphadenopathy



Necrotizing lymphadenitis?







Langerhans cell histiocytosis of the lymph node

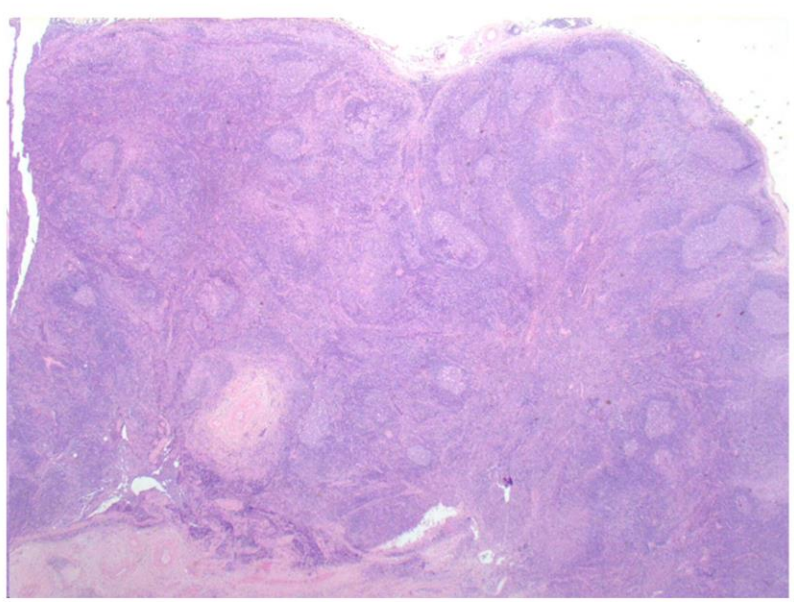
Sheets of LC and eosinophils, frequently eosinophilic abscesses

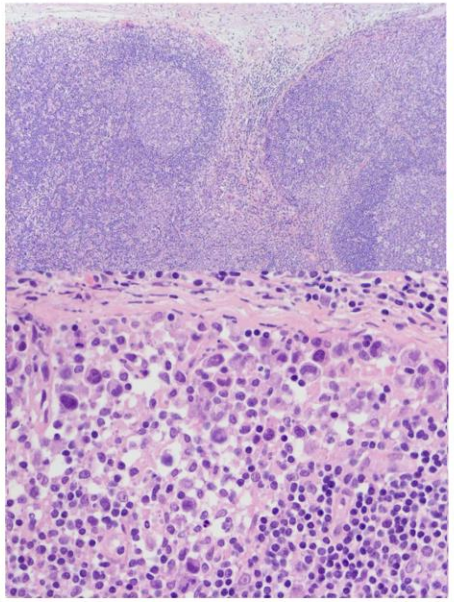
CD1a+, Langerin+, S100+

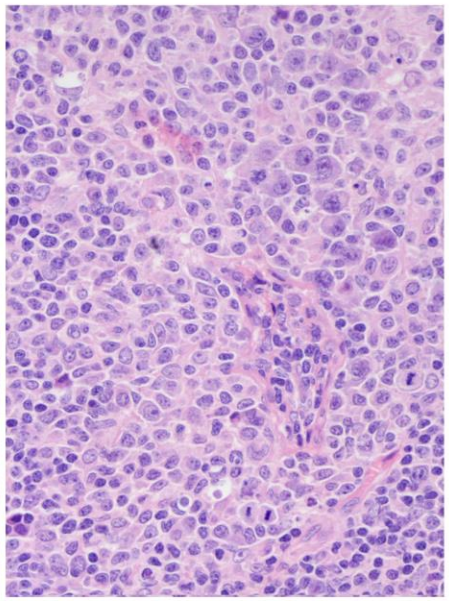
BRAF mutations in 50%, MAP2K1 mutations in 25-30%

ALCL, ALK+

30-year-old female, inguinal lymph node,
History of lymphoma 15 years ago.







Reactive disorders mimicking malignant lymphoma

- Infectious mononucleosis and other EBV-associated LPD
- florid atypical interfollicular hyperplasia (e.g. drug-associated)
- Progressive transformation of germinal centers
- Necrotizing histiocytic lymphadenitis (Kikuchi-Fujimoto)
- Herpes simplex lymphadenitis
- Atypical marginal zone hyperplasia

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A stepwise approach to difficult reactive cases

- Clinical history!
  - Age, sex, preexisting conditions
  - Onset of symptoms
  - Generalized/localized lymphadenopathy
  - Previous material and history
- Morphology
  - Good, well stained sections!
  - Systematic approach based on architecture
  - Low magnification!
- Immunohistochemisty
  - Determination of dominant cell type (B vs. T, plasma cells), immunoarchitecture, light chain restriction
  - Detemination of aberrant immunophenotype (CD5, CD23, cyclin D1, CD43, CD30)
  - Start with a screening panel (CD20, CD3, CD23, IGD, MIB1)
- Molecular diagnostics often will **NOT** solve problem