VII CORSO del GRUPPO ITALIANO DI EMATOPATOLOGIA

La DIAGNOSTICA EMATOPATOLOGICA nell'ERA della MEDICINA di PRECISIONE

Lymphadenopathy and Lymphoproliferative disorders in Inborn Errors of Immunity (IEI): clinical case

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- The authors have no disclosures to declare

CLINICAL CASE

M.C. ♀

Healthy parents and two older brothers

7 Y.O. (06/2018)

Left lateral cervical (LTC) lymphadenomegaly

08/2018

Oral Amoxiclav

US: **Hypoechoic** lymph node package with **high vascularization**

10-12/2018

Left lateral cervical **lymphadenectomy**

Borderline lymphoma

PET-FDG & CT: **Stage IIA** involvement (left and right LTC chains) (**VUS 12**)

01/2019

3 cycles of **CVP**

PET-FDG & CT: persistent FDG-uptake in the left submandibular lymphadenopathy (**VUS 8**)

02/2019 - 10/2020

Serial ultrasound evaluations indicated **stable lymphadeno-pathy**

12/2020

Right submandibular/ submental **lymphadenectomy**

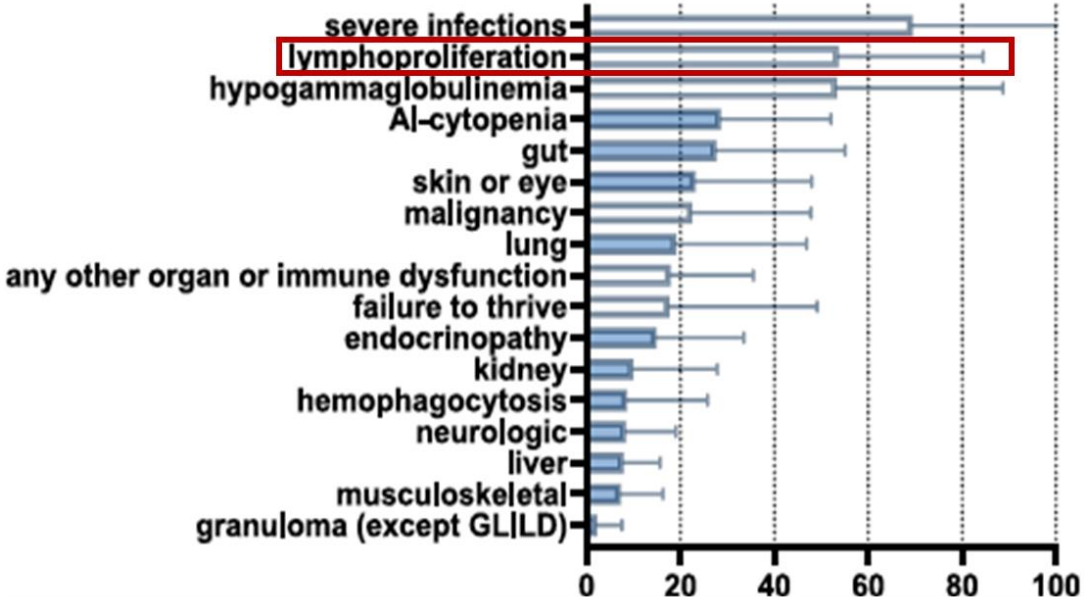
Left inguinal and right iliac **lymphadenectomy**

Follicular hyperplasia with partial borderline lymphoma

Mixed reactive lymphoid hyperplasia (left) and PTGC (right)

PET-FDG & CT: **multisite involvement:** parotid, jugulo-digastric, submandibular, lateral cervical, and inguinal regions

LYMPHOPROLIFERATIVE DISORDERS (LPDs) AS THE SECOND MOST COMMON CLINICAL FEATURE IN INBORN ERRORS OF IMMUNITY (IEIs)



Seidel MG, Hauck F J Allergy Clin Immunol. (2024)

Red flags for IEI-related LPD

- Chronic or recurrent course ✓
- Atypical sites (e.g., pulmonary involvement) X
- Family history of LPDs or IEIs X
- Severe/persistent EBV infection X
- Early-onset or refractory immune dysregulation ✓
- Abnormal immunological profile ?

IMMUNOLOGICAL WORK UP

M.C. ♀

CD3+ 72% (1656/mmc)
CD4+ 42% (965/mmc)
Naïve CD4+ 62%
EMRA CD4+ 9%
CD8+ 22% (506/mmc)
↑ Naïve CD8+ 64%
↓ EM CD8+ 13%
TEMRA CD8+ 16%
CD3+ gamma/delta 7%
↓ CD16CD56+ 4% (92/mmc)

Normal lymphoproliferation T test

B tot 19.6% (451/mmc)
↑ B naïve 88%
B Memory IgD+ 6%
↓ B Memory switched IgD- 4%
↓ Transitional CD38++IgM++ 3%

IGG 791 mg/dl
IGA 55 mg/dl
IGM 78 mg/dl
↓ IGG1 353 mg/dl
↑ IGG4 129 mg/dl

Negative CMV/EBV viremia

Negative EBER

CVID-LIKE SUSPICION

Negative NGS panel for IEI (56/508 genes)

PS6 Phosphorylation on CD3+
5.84% (nv 2,6-17.4%)

PS6 Phosphorylation on CD19+
1.5% (nv 2,2-26,4%)

Histologic revision of initial borderline lymphoma

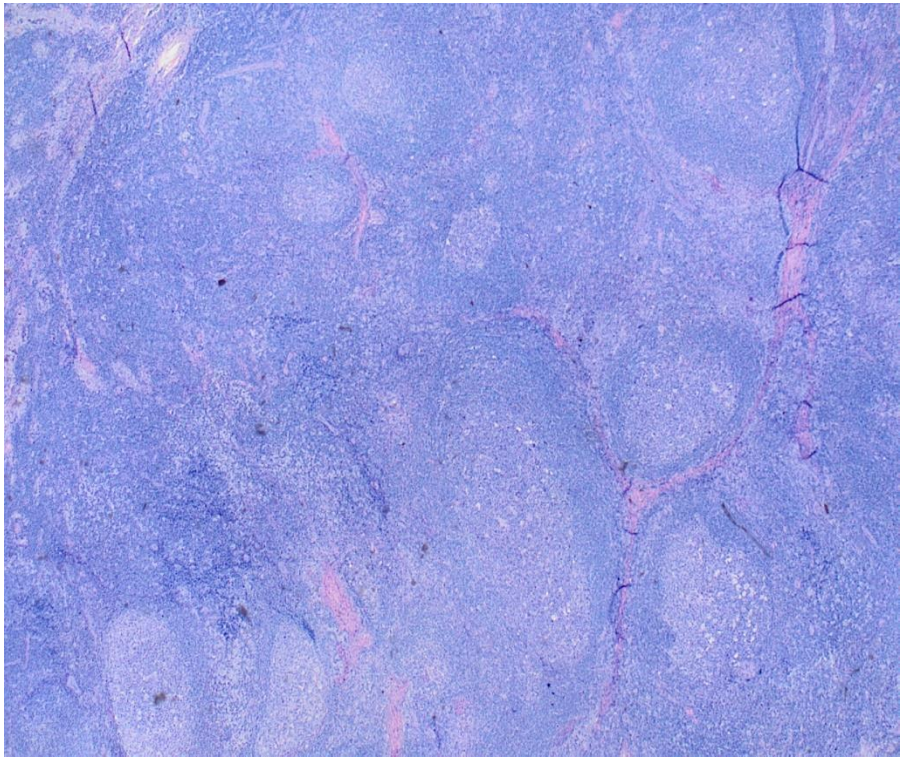
OPEN QUESTIONS

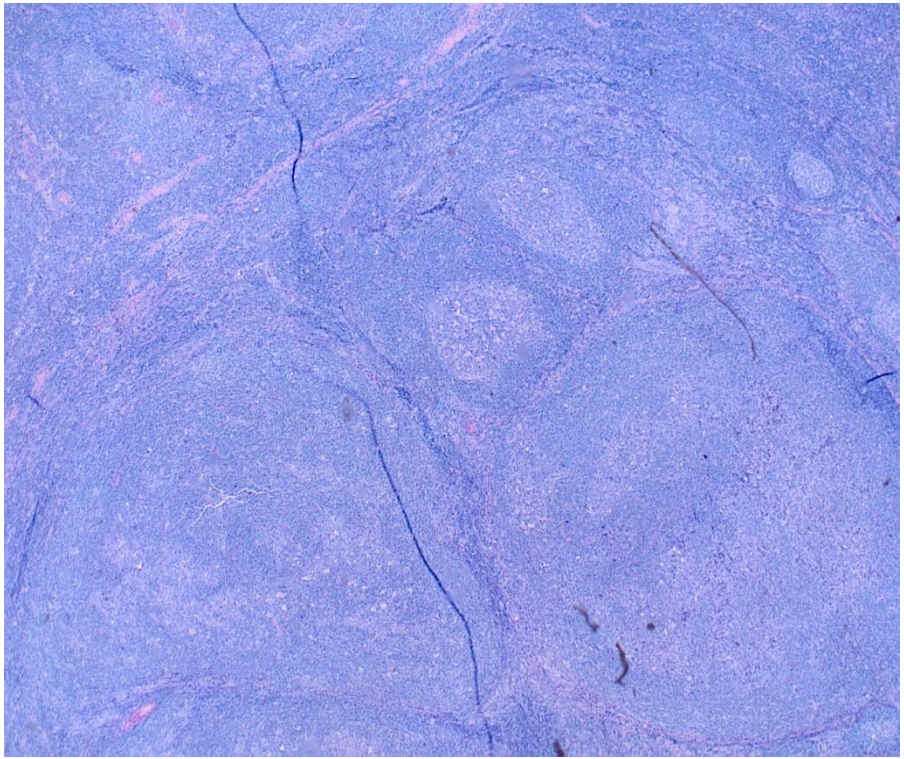
What are the optimal protocols for long-term immunological monitoring

Is a repeat NGS panel for IEI indicated after a period of time?
Should we perform a WES/WGS?

Which histopathological features can reliably distinguish IEI-related LPD from overt malignant LPD?

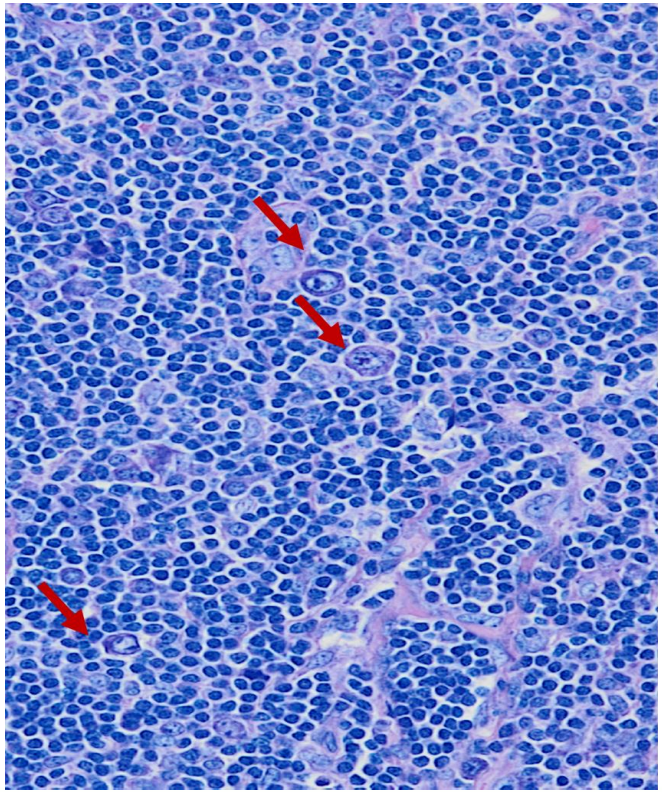
2018: cervical lymph node

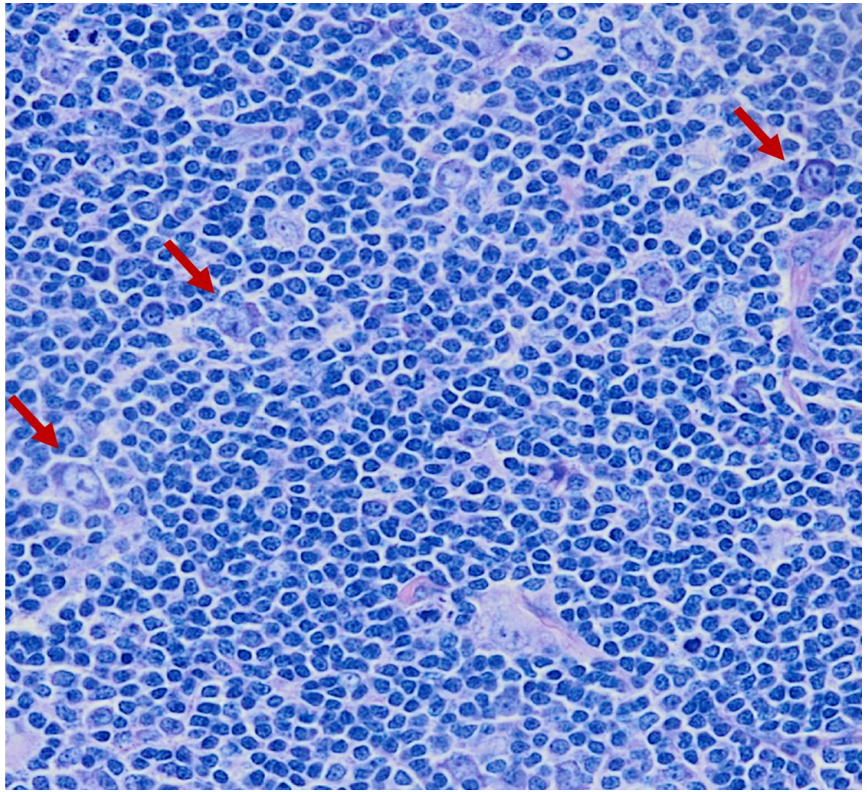




Structure preserved; occasional expanded follicoles with early features of progressive tranformation

1° biopsy: cervical lymph node: isolated dispersed mononucleated large cells with atypical cytology, but not totally/fully/always consistent with LP cells (more often centroblast like)





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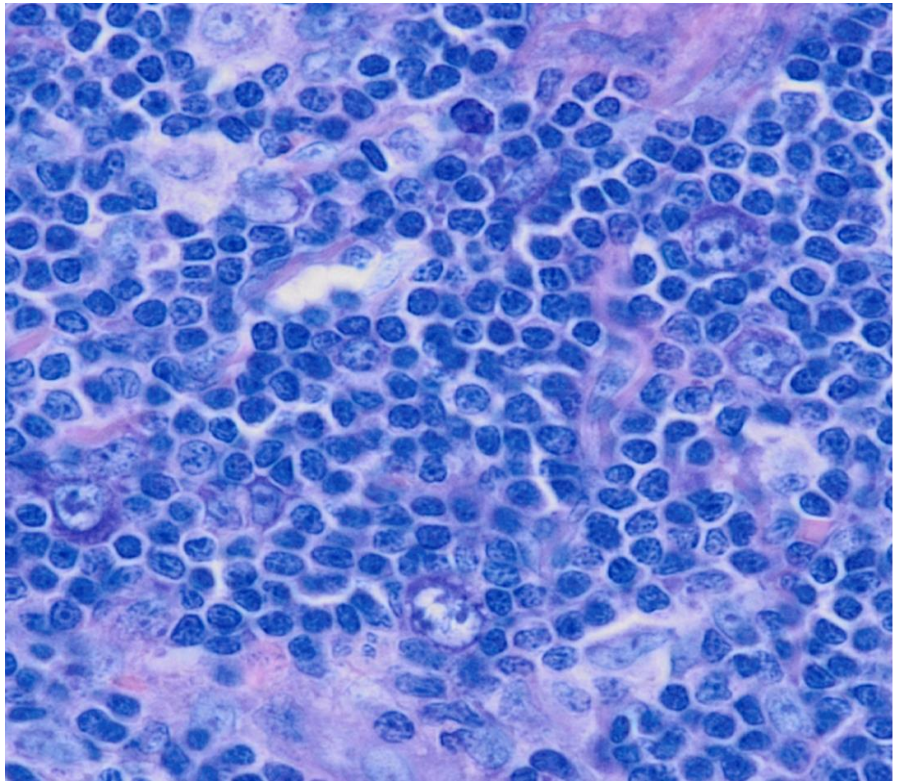
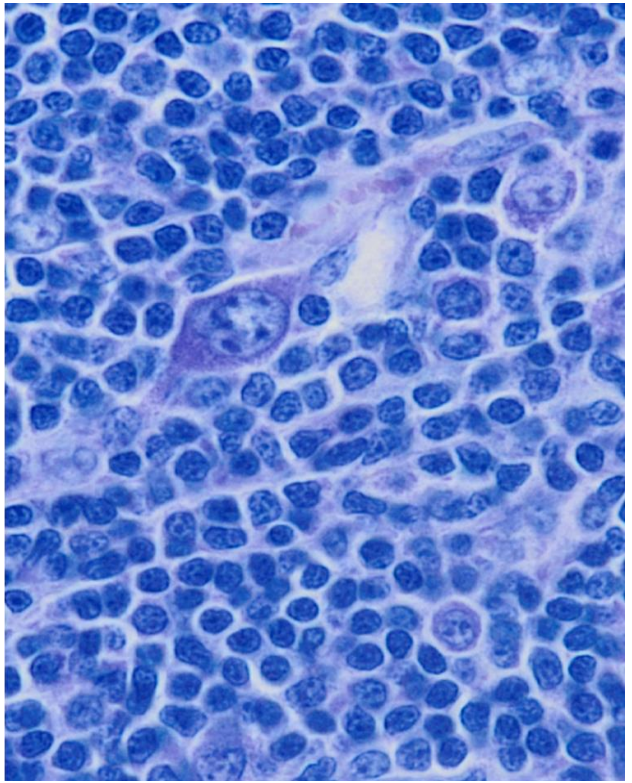
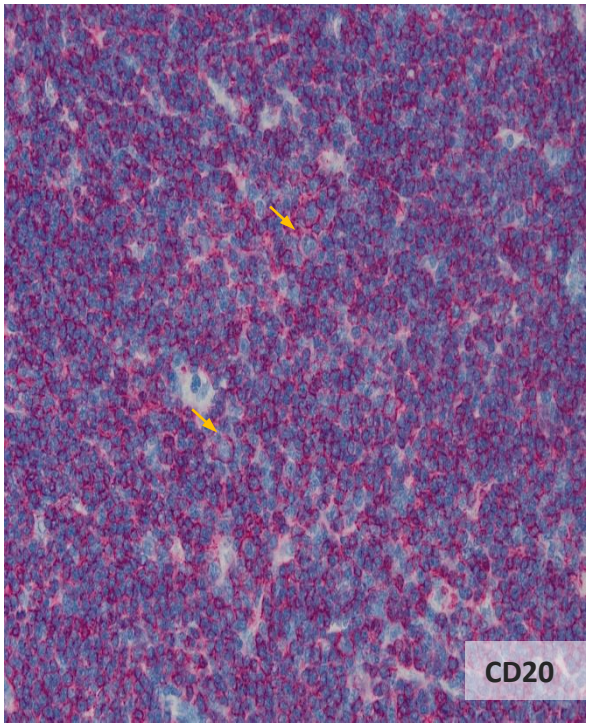
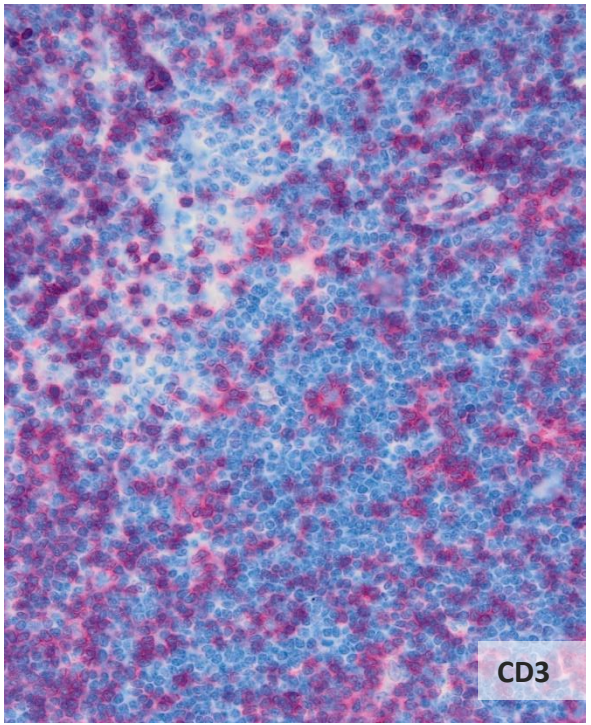


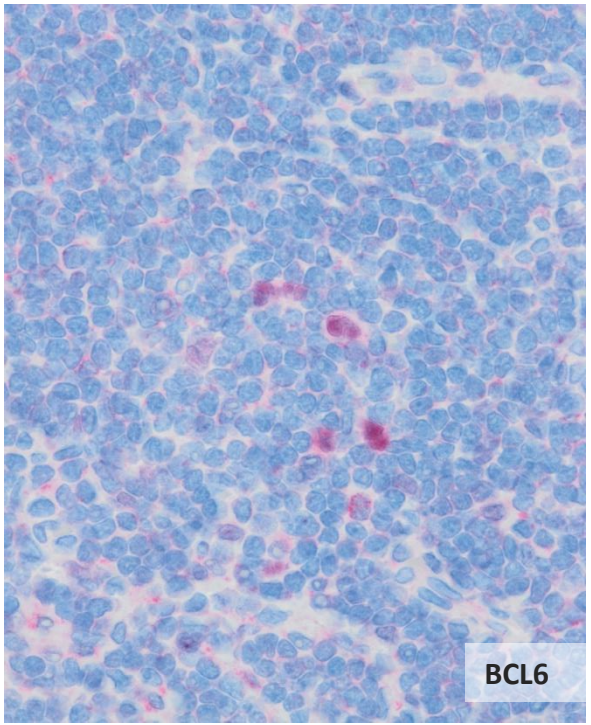




CD20+ in the transformed follicles; some large cells



CD3+ T cells dispersed in the mantle zone of transformed follicles; some rosetting (also **PD1+**)



BCL6 +, CD10-, CD30 rare+, CD15-, EBER -

Final diagnosis (2018):

"Findings **borderline** between partial involvement by **NLPHL** and atypical **follicular hyperplasia with PTGC features**". Slightly favoured first option.

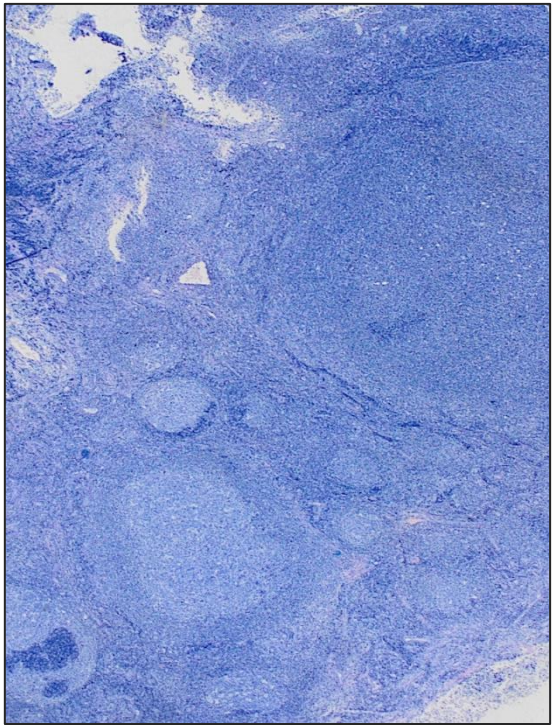
- CHT: 3 cycles of **CVP** (cyclophosphamide, vincristine, prednisolone)

2020 → relapse of cervical/submandibular bilateral lymphoadenopathy: 2 biopsies of submental lymph nodes:

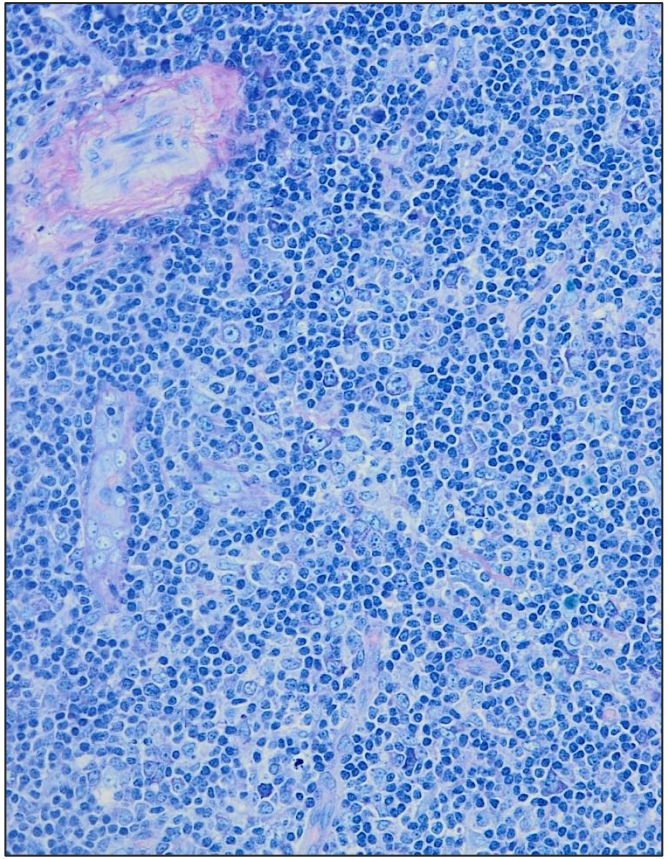
- One showed **follicular hyperplasia** without features of follicle/GC transformation

- One showed …

2018: submental lymph node

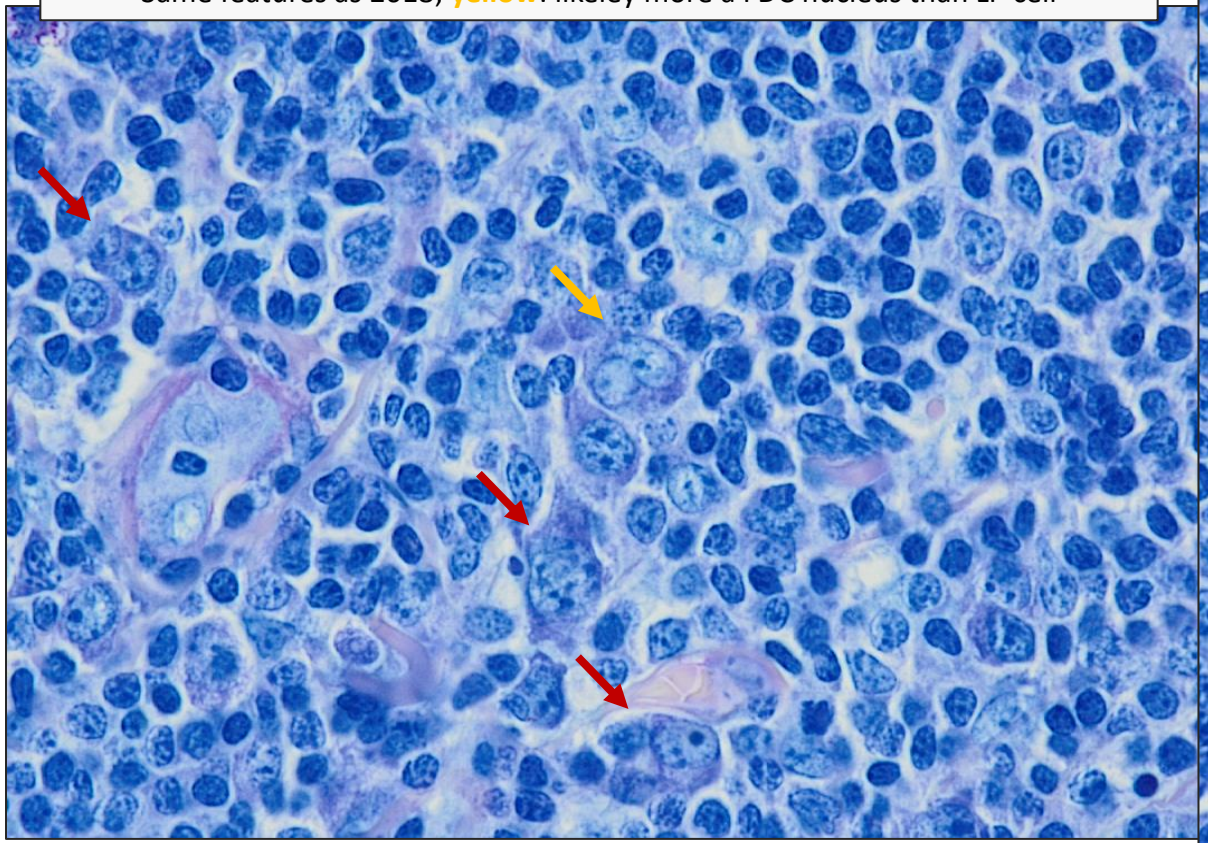


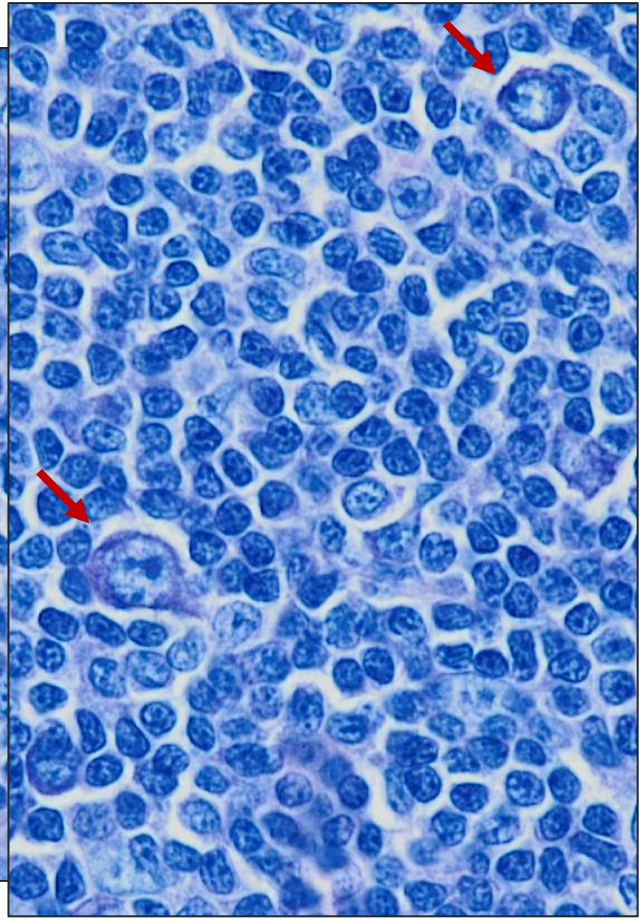
2020: structure preserved; occasional expanded follicoles with early features of progressive tranformation

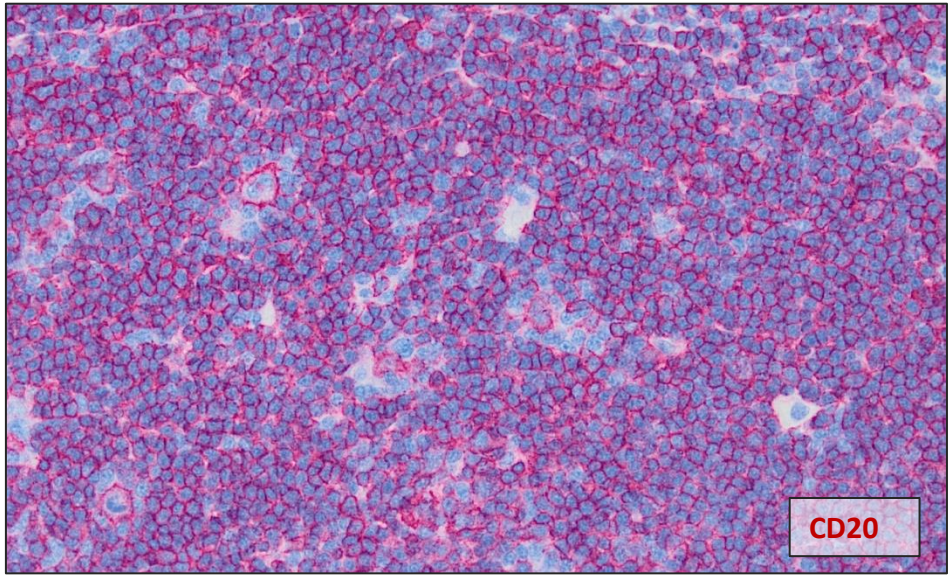


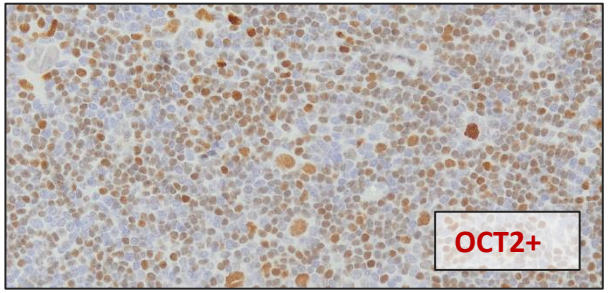
Isolated dispersed mononucleated large cells

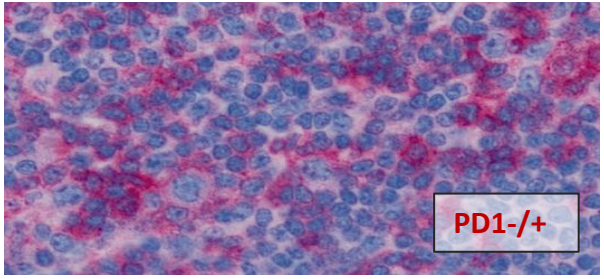
Same features as 2018; yellow: likeley more a FDC nucleus than LP cell

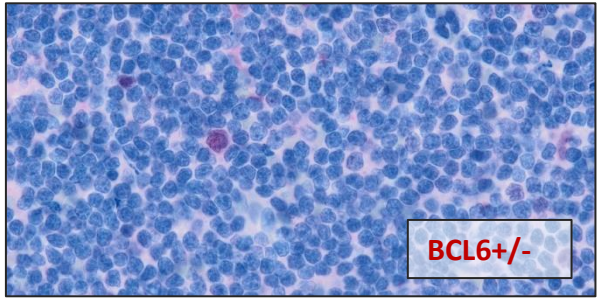


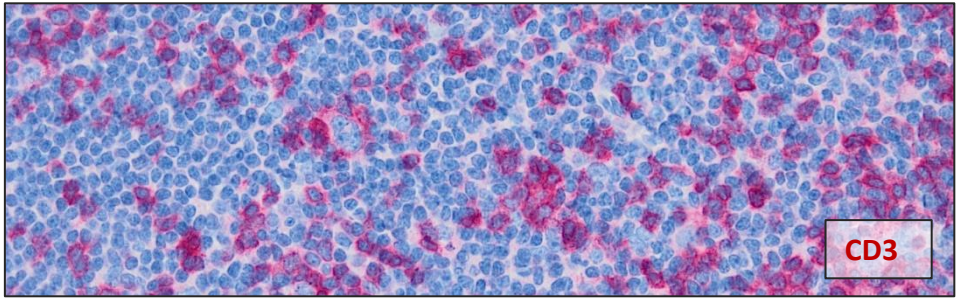












CD30-
CD15-
EMA-
EBER-
CD10-

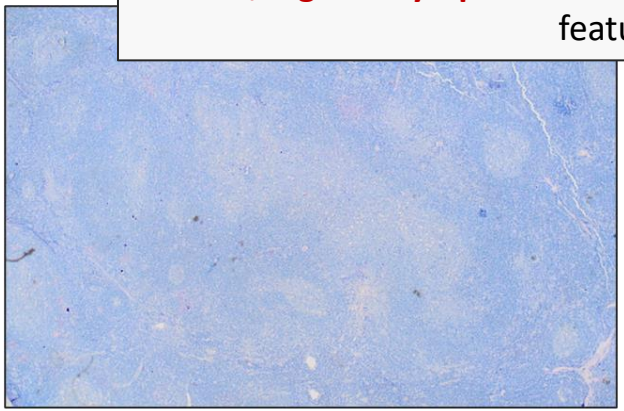
Final diagnosis **(2020): Borderline** findings between partial involvement by **NLPHL** with an intrafollicular/follicular growth pattern and **follicular hyperplasia with PTGC features**. **Again favoured 1° option, still limited involvement and similar features to those observed in 2018.**

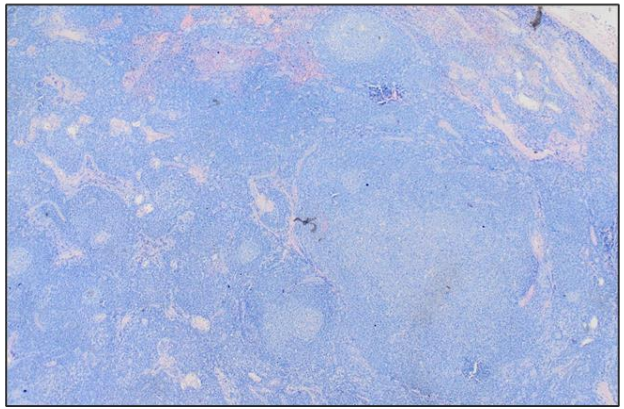
- Restaging (PET and CT): additional lymphadenopathies; no further treatment.

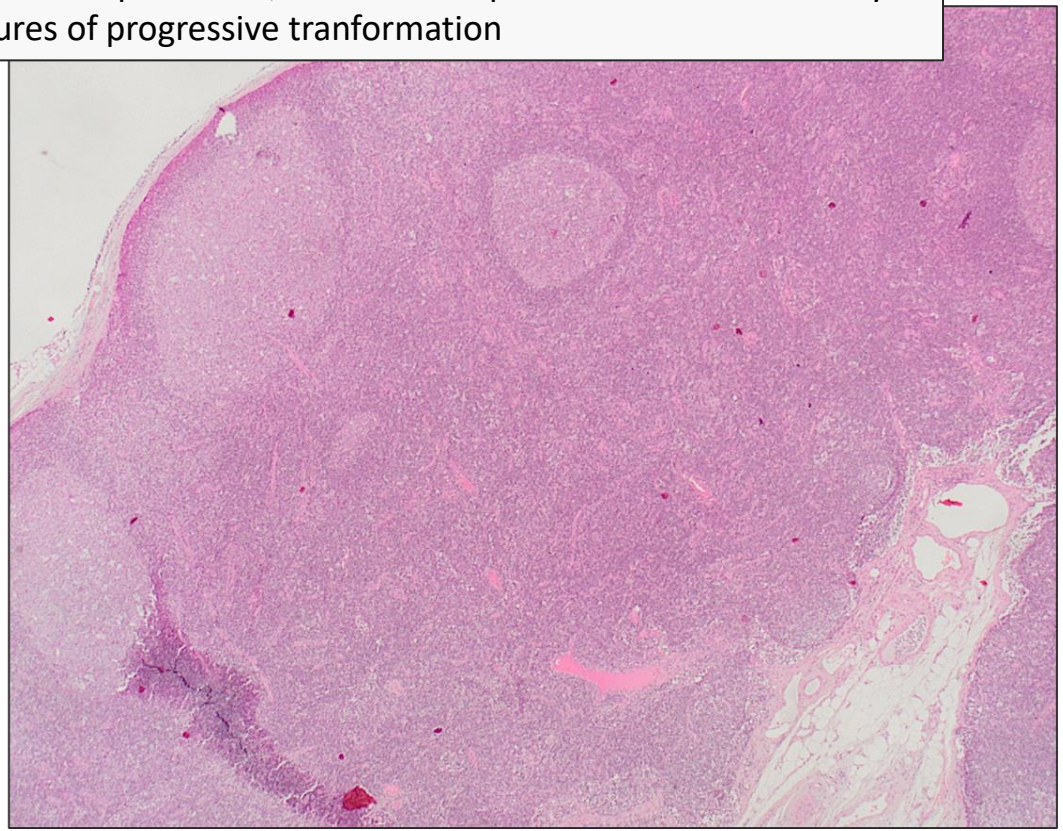
2021 → Biopsy of inguinal lymph nodes

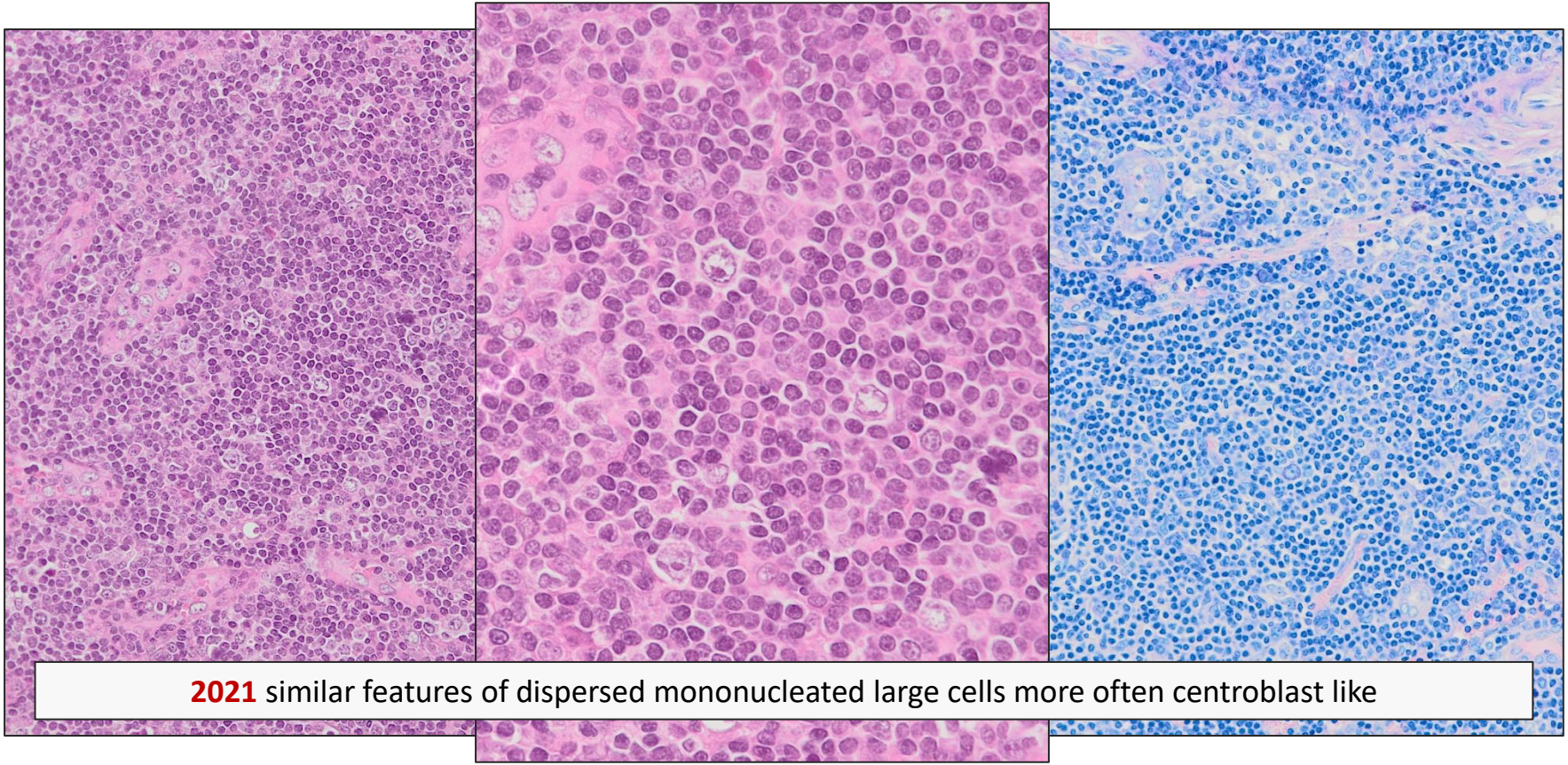
the patient underwent 3 lymph node biopsies in 4 years!

2021; inguinal lymphnode: structure preserved; occasional expanded follicles with early features of progressive tranformation

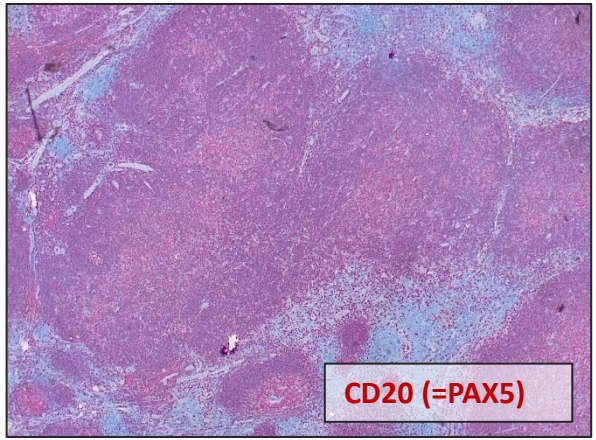


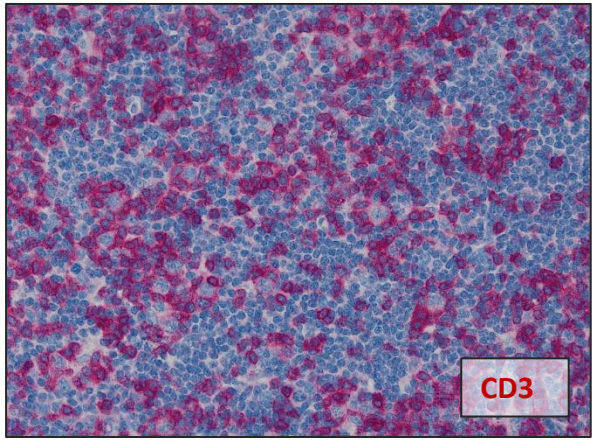




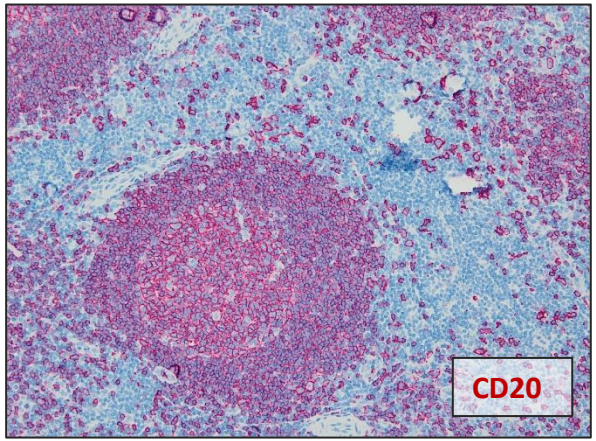


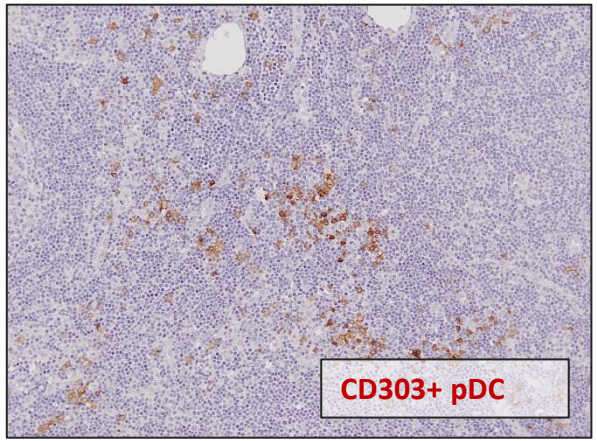
2021 similar features of dispersed mononucleated large cells more often centroblast like





Large cells **CD20+/CD30+** outside the follicles with similar cytology than those previously observed, but **BCL6-/CD10-**
Variable IRF4





CD30+
CD15-
OCT2+
EBER-

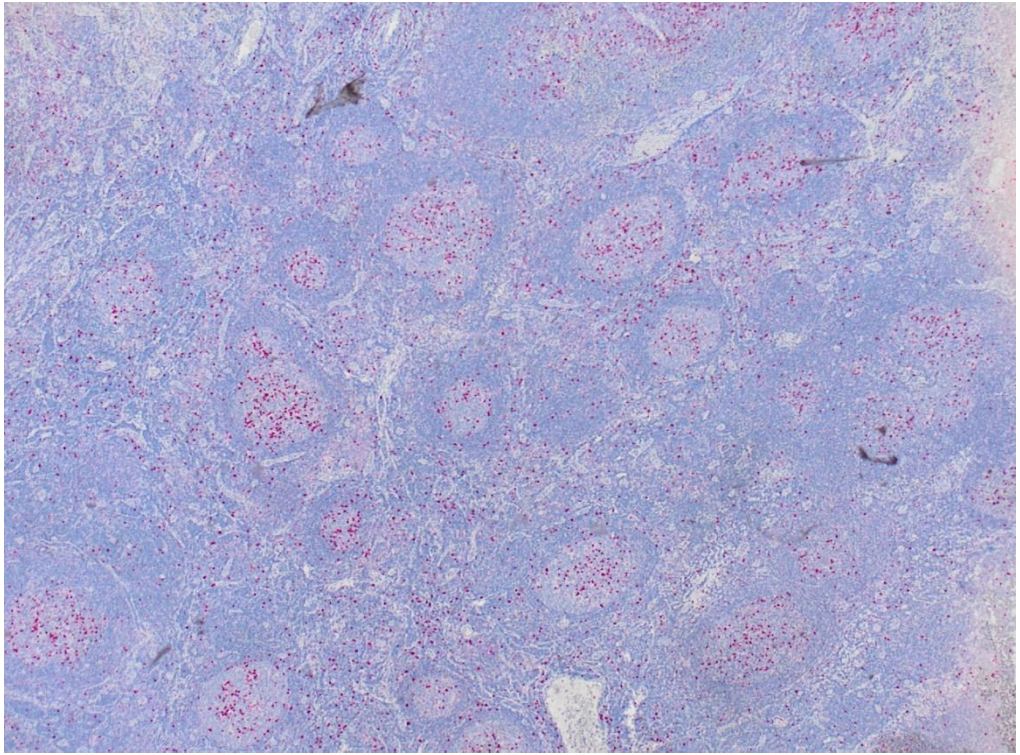
Final diagnosis (2021)

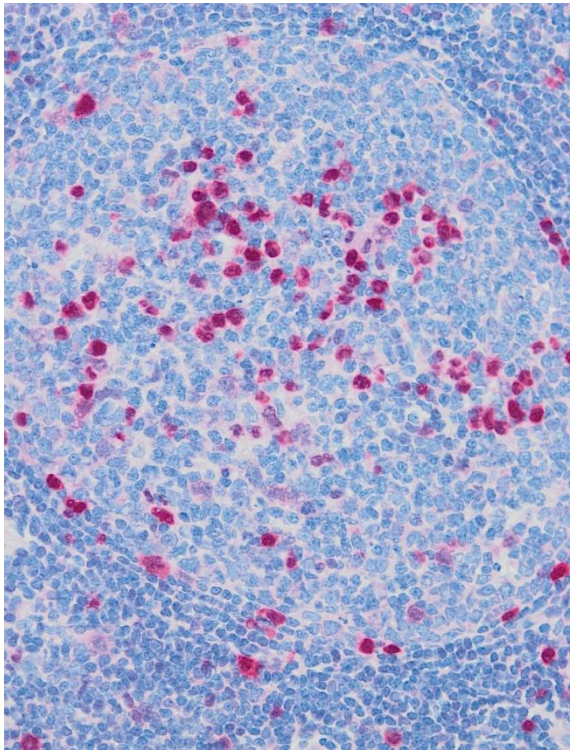
Lymph node with focal progressively transformed germinal centers (**PTCGs**).
Insufficient findings for a diagnosis of lymphoma.

→ Immunological **re-evaluation** and **follow-up**

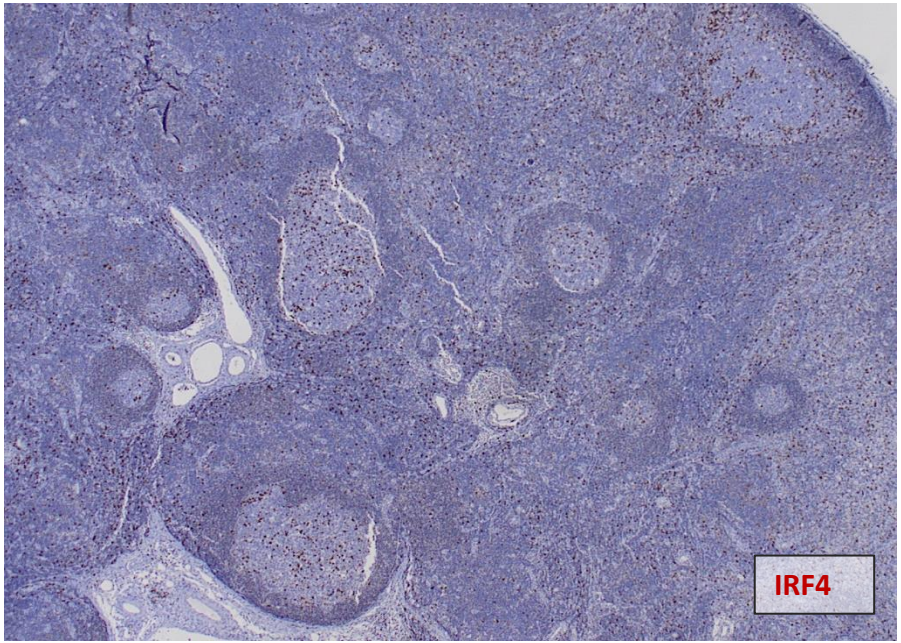
→ Retrospective review of the cases

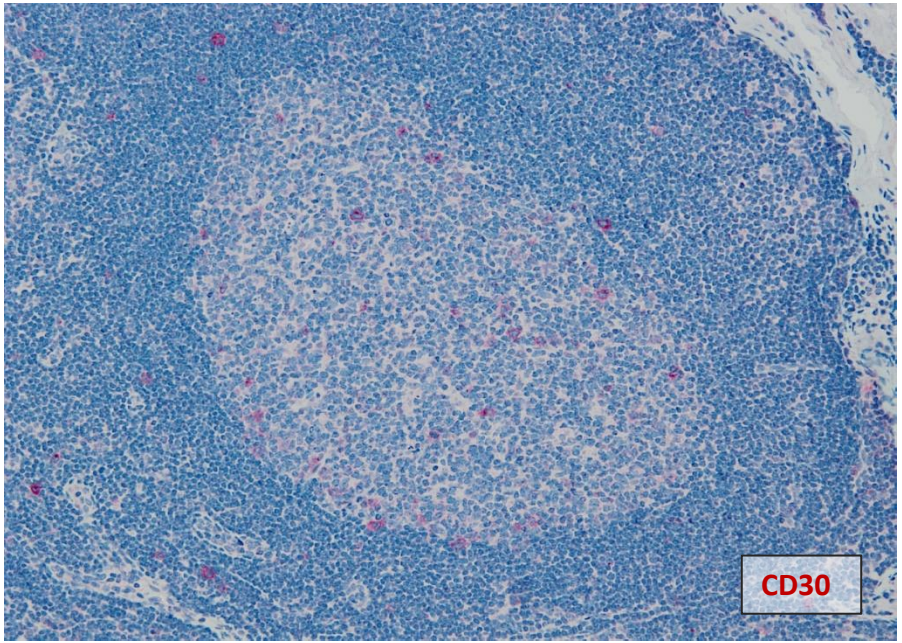
Residual reactive lymph node parenchyma (all biopies)



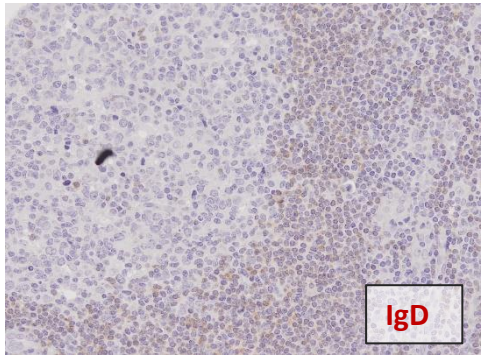


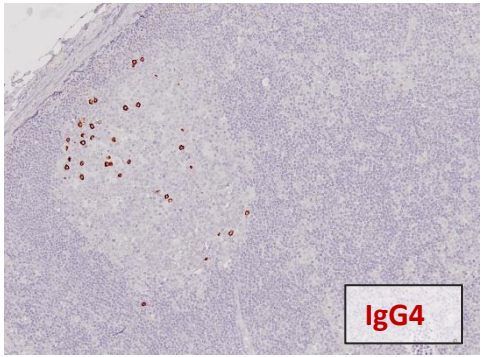
Uncommonly **higher number of IRF4+ cells within GC**; CD138 -+ weak; interpreted as temptative early intra GC- plasma cells differentiation

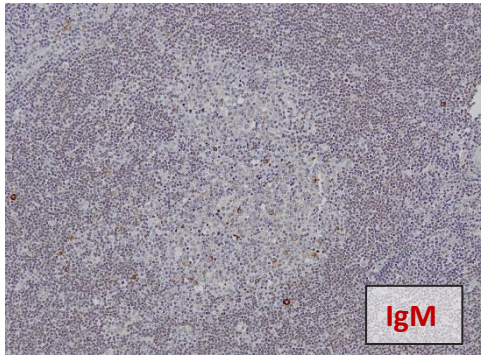

IRF4

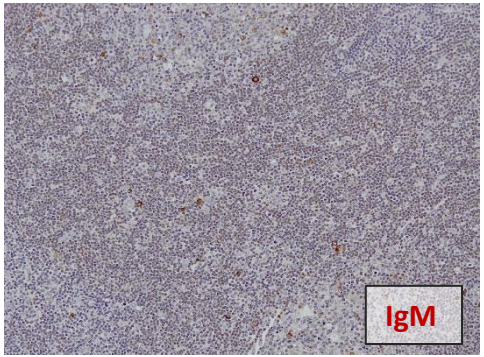

CD30

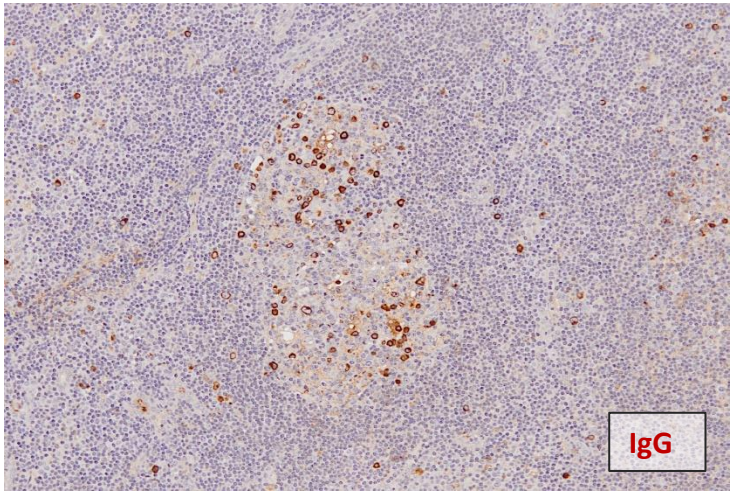
Heavy chain phenotype











- ✓ Similar **heavy chain phenotype** could be observed in the GC and in interfollicular areas (IgG predominant, IgM few, IgD almost absent)
- ✓ We could **not correlate** heavy chain phenotype to the immunologic alterations

Take-home messages

PTGC observed in immune dysregulation conditions in roughly **24%** cases including SLE, IgG4RD, Castleman disease, ALPS, refractory Evans syndrome; reported also in few CVID patients

In our case it is likely the patient really never had a "true" PLHL

Increase in plasma-cell differentiating B cells within GCs is atypical and may suggest an **early/premature switch to plasma cell differentiation within GC where it should not occur.**
this pattern is not uncommonly observed in other acquired dyregulation conditions (IgG4RD, CD)

Both features should warrant referral of the patient for an immunological evaluation (either inborn or acquired)

Sato et al, Mod Pathol 2012; Shaikh F et al. Pediatr Blood Cancer. 2013; Keyrouz et al. Cureus 2026

Thank you for your attention