VII CORSO del GRUPPO ITALIANO DI EMATOPATOLOGIA

La DIAGNOSTICA EMATOPATOLOGICA nell'ERA della MEDICINA di PRECISIONE

Lymphoproliferative Disorders in Inborn Errors of Immunity: Clinical Case

Matilde Callegarin

Pathology Unit, Department of Medicine - DIMED, University of Padua School of Medicine, Via Giustiniani 2, 35128 Padua, Italy

Bologna, Aula Prodi | 11-12 maggio 2026

Clinical history

Female, 10y

- ALPS-like syndrome with heterozygous mutation of *ORAI1*
- Recent EBV infection
- Persistent left latero-cervical lymphadenopathy; splenomegaly
- No systemic symptoms

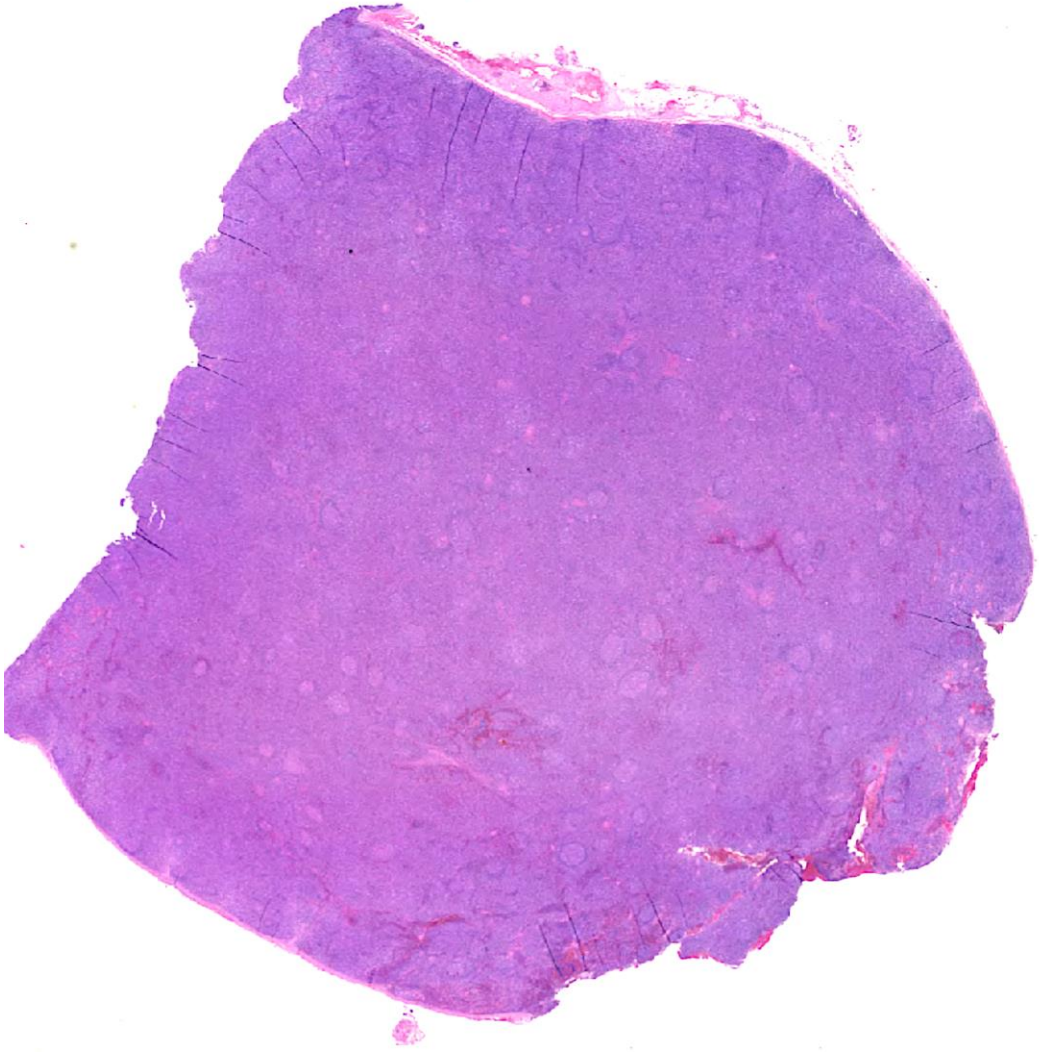
Clinical history

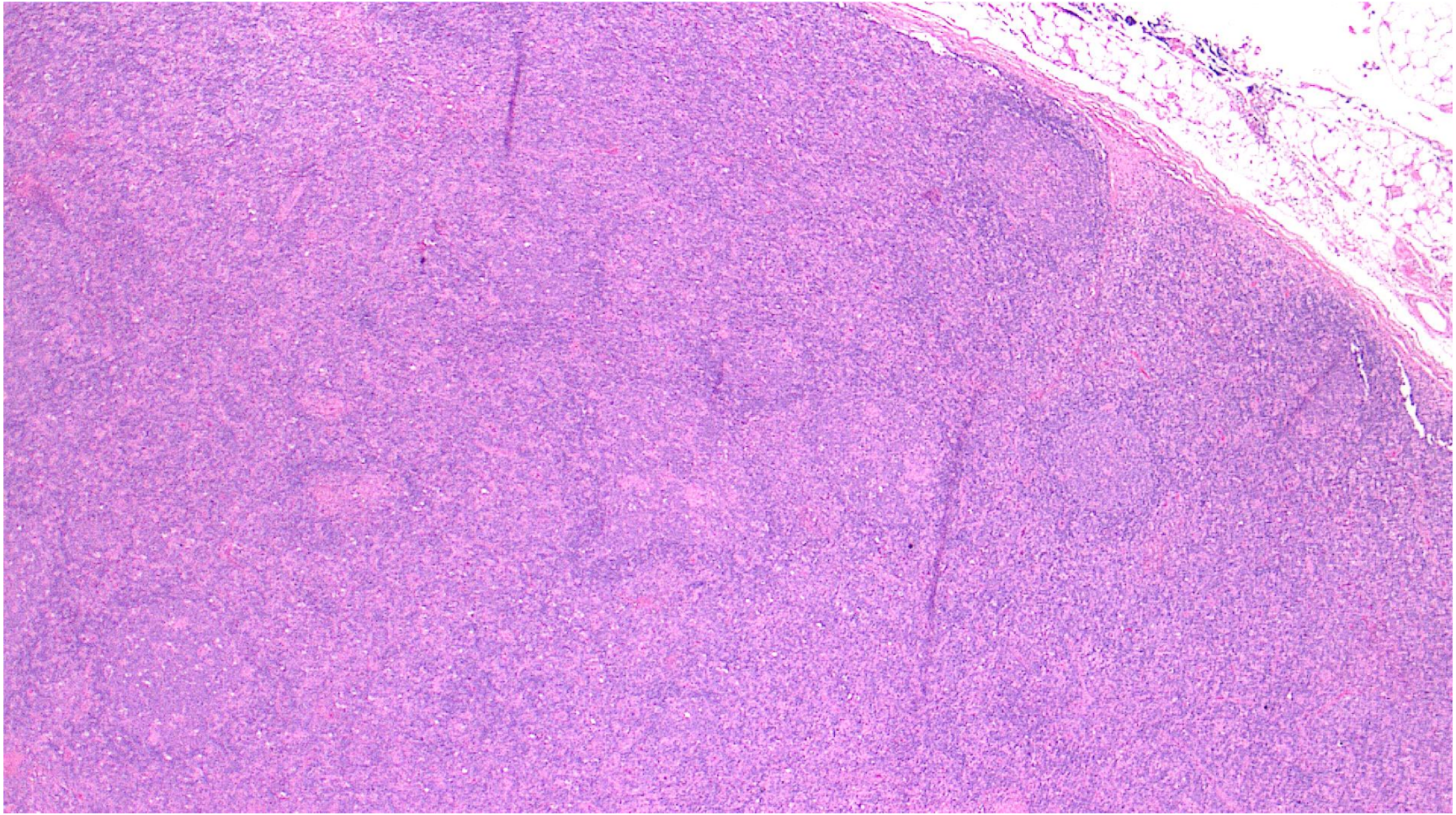
Female, 10y

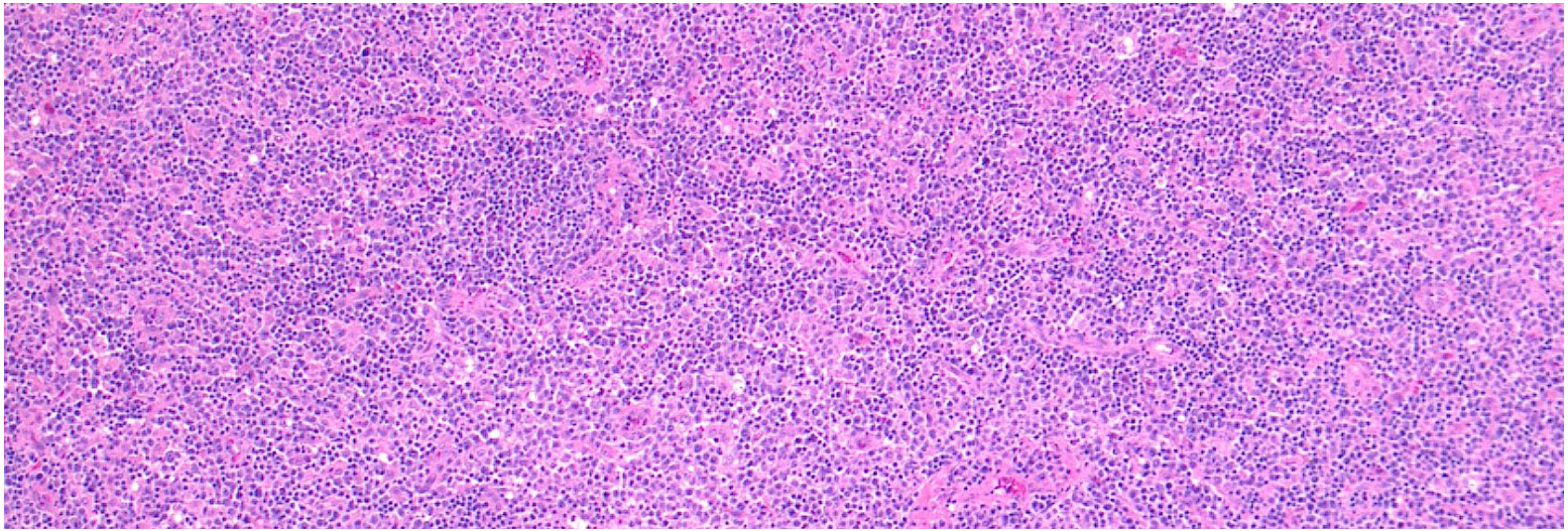
- ALPS-like syndrome with heterozygous mutation of *ORAI1*
- Recent EBV infection
- Persistent left latero-cervical lymphadenopathy; splenomegaly
- No systemic symptoms

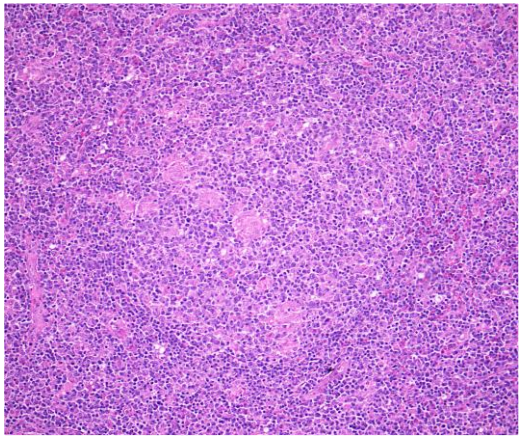
Laboratory tests

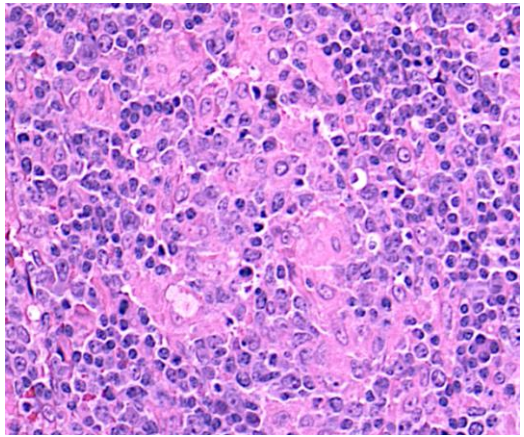
- Hb= 112 g/L
- WBC= 7.24 $x10^9$L
- PLTS= 337 $x10^9$L
- Expansion (8%) of $CD4^-/CD8^-$ T-cells

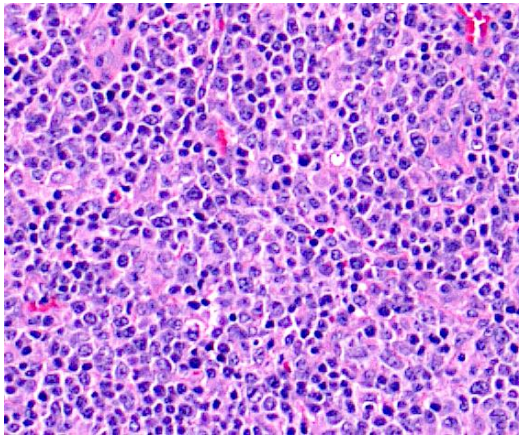


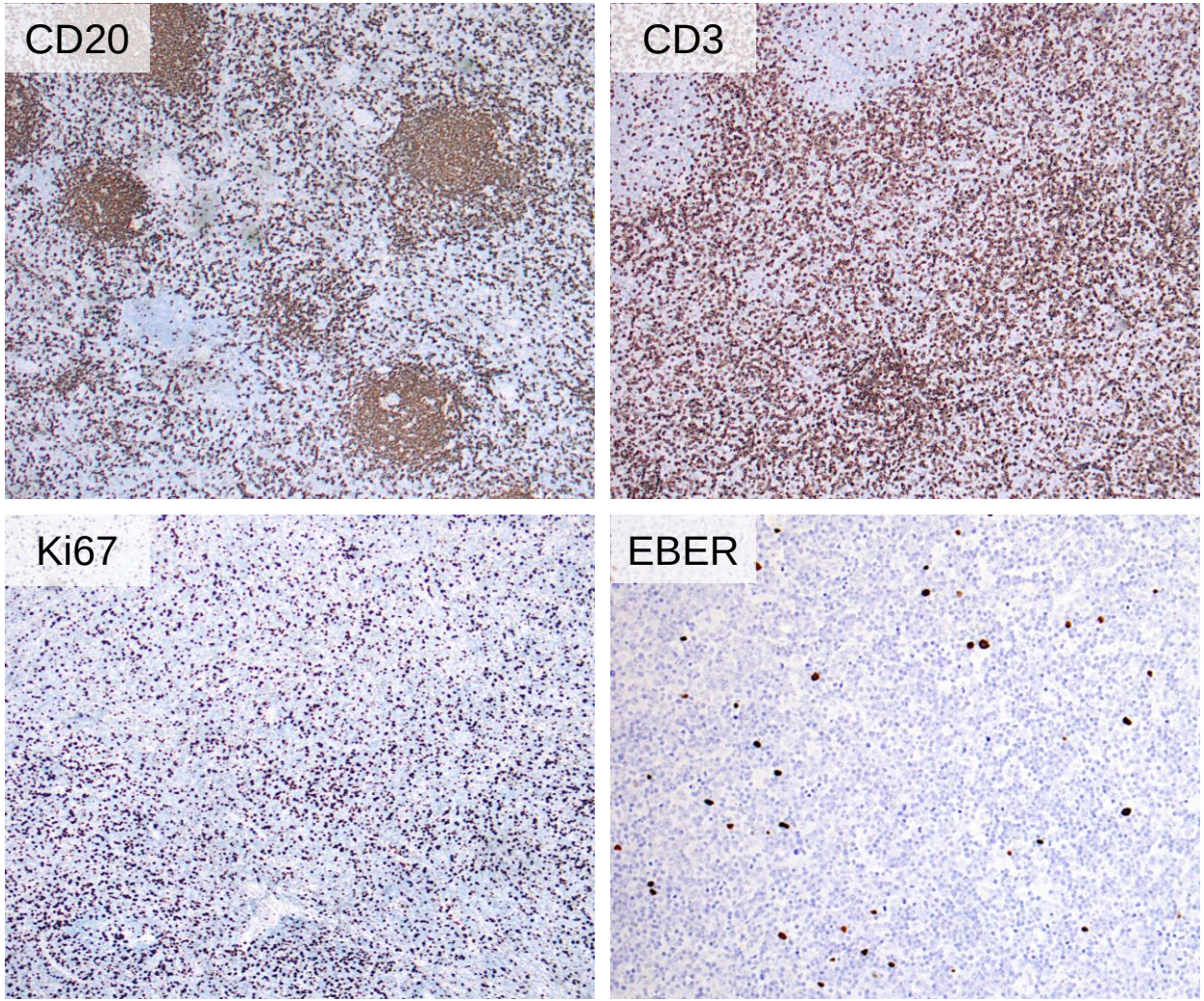


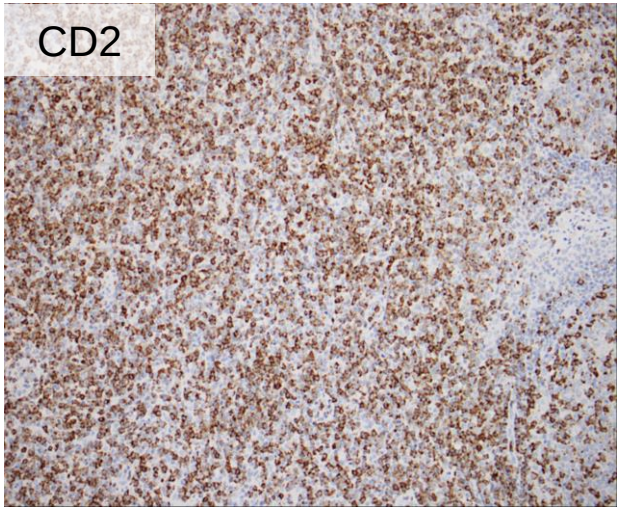


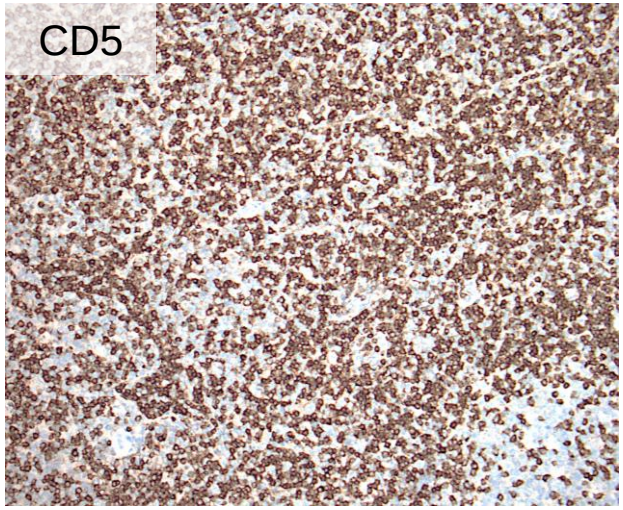


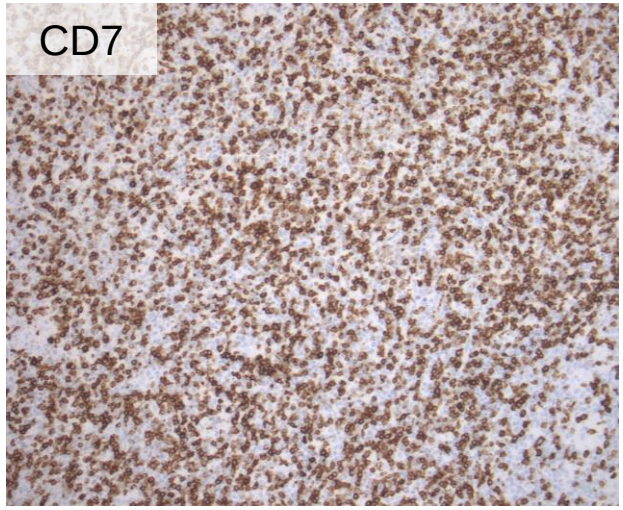


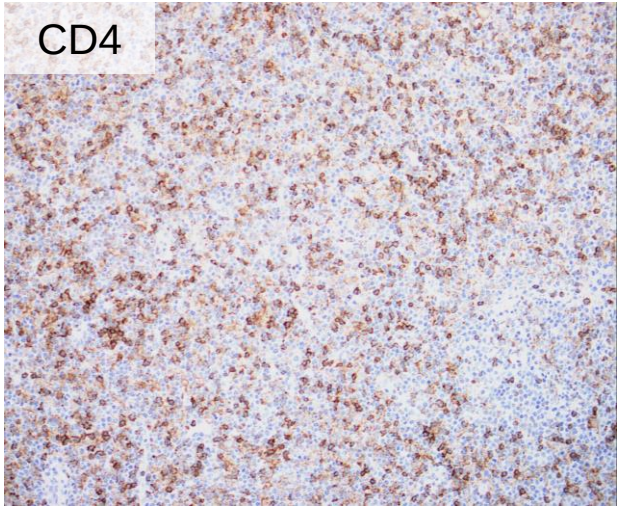


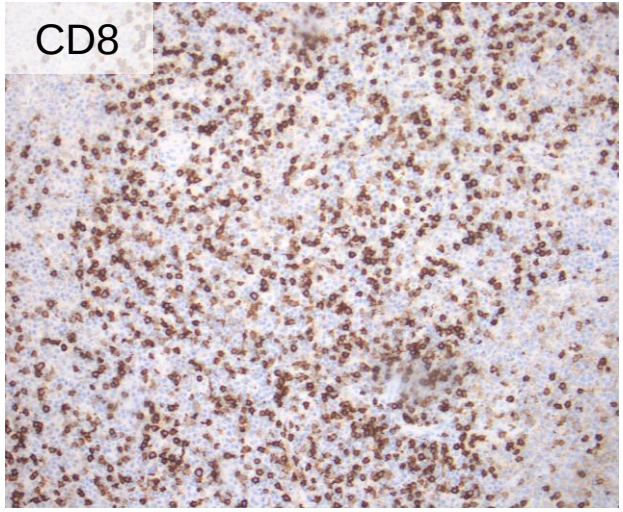

CD20
CD3
Ki67
EBER

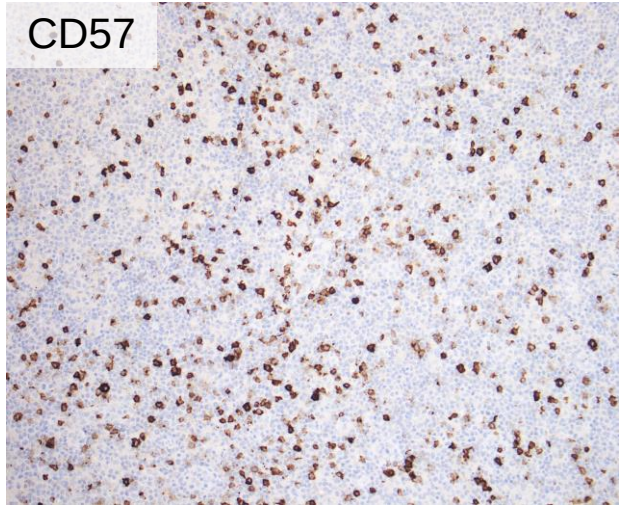

CD2

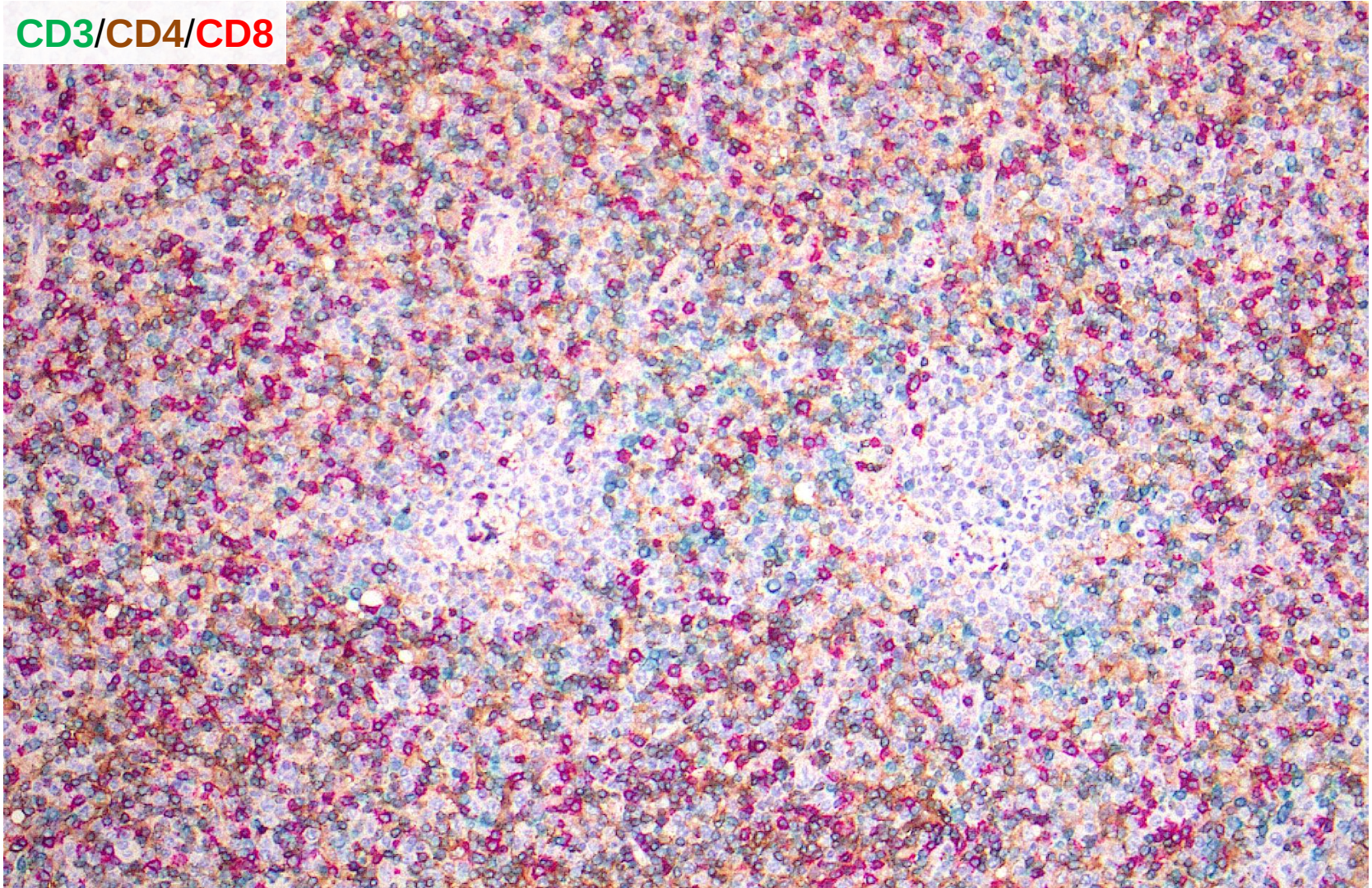

CD5


CD7


CD4

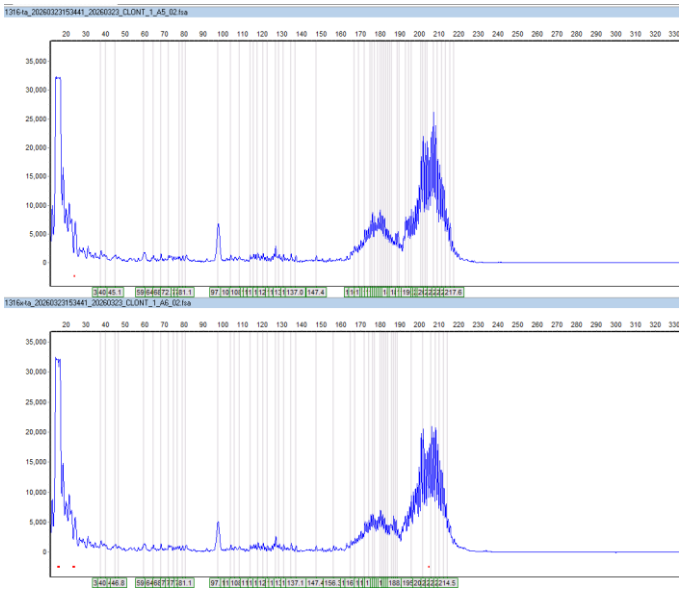

CD8

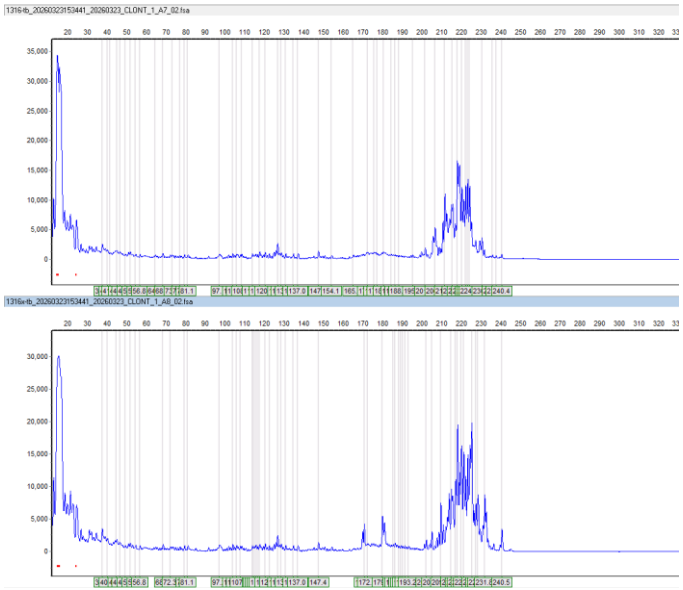

CD57


CD3/CD4/CD8

Molecular tests

Polyclonal *TR* gene rearrangement





Final diagnosis

Lymphoid hyperplasia with paracortical expansion and increase of DNT cells in the setting of immunodeficiency/dysimmunity

Autoimmune lymphoproliferative syndrome (ALPS) and related disorders

ALPS is a genetic disorder characterised by **autoimmunity** and **lymphoproliferations** associated with mutations in genes involved in **FAS-mediated apoptosis**.

Previous nomenclature	Revised nomenclature	Definition
ALPS type 0	ALPS-FAS	Patients fulfill ALPS diagnostic criteria and have germline homozygous mutations in *FAS*.
ALPS type Ia	ALPS-FAS	Patients fulfill ALPS diagnostic criteria and have germline heterozygous mutations in *FAS*.
ALPS type Im	ALPS-sFAS	Patients fulfill ALPS diagnostic criteria and have somatic mutations in *FAS*.
ALPS type Ib	ALPS-FASLG	Patients fulfill ALPS diagnostic criteria and have germline mutations in FAS ligand.
ALPS type IIa	ALPS-CASP10	Patients fulfill ALPS diagnostic criteria and have germline mutations in caspase 10.
ALPS type III	ALPS-U	Patients meet ALPS diagnostic criteria; however, genetic defect is undetermined (no FAS, FASL, or CASP10 defect).

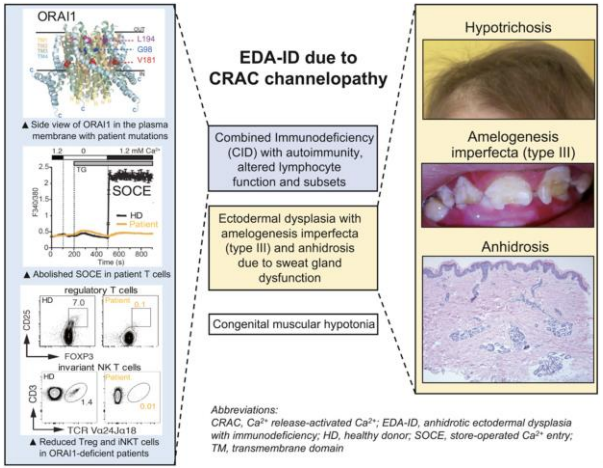
Autoimmune lymphoproliferative syndrome (ALPS) and related disorders

ALPS is a genetic disorder characterised by **autoimmunity** and **lymphoproliferations** associated with mutations in genes involved in **FAS-mediated apoptosis**.

Previous nomenclature	Revised nomenclature	Definition
ALPS type 0	ALPS-FAS	Patients fulfill ALPS diagnostic criteria and have germline homozygous mutations in *FAS*.
ALPS type Ia	ALPS-FAS	Patients fulfill ALPS diagnostic criteria and have germline heterozygous mutations in *FAS*.
ALPS type Im	ALPS-sFAS	Patients fulfill ALPS diagnostic criteria and have somatic mutations in *FAS*.
ALPS type Ib	ALPS-FASLG	Patients fulfill ALPS diagnostic criteria and have germline mutations in FAS ligand.
ALPS type IIa	ALPS-CASP10	Patients fulfill ALPS diagnostic criteria and have germline mutations in caspase 10.
ALPS type III	ALPS-U	Patients meet ALPS diagnostic criteria; however, genetic defect is undetermined (no FAS, FASL, or CASP10 defect).

ALPS-LIKE SYNDROMES

Dysimmune disorders with clinical and laboratory features of ALPS but genetic **defects outside the Fas–FasL** pathway



Diagnostic criteria of ALPS

Required

1. Chronic (> 6 months), nonmalignant, noninfectious lymphadenopathy or splenomegaly or both
2. Elevated $CD3^+TCR\alpha\beta^+CD4^-CD8^-$ DNT cells (≥ 1.5% of total lymphocytes or 2.5% of $CD3^+$ lymphocytes) in the setting of normal or elevated lymphocyte counts

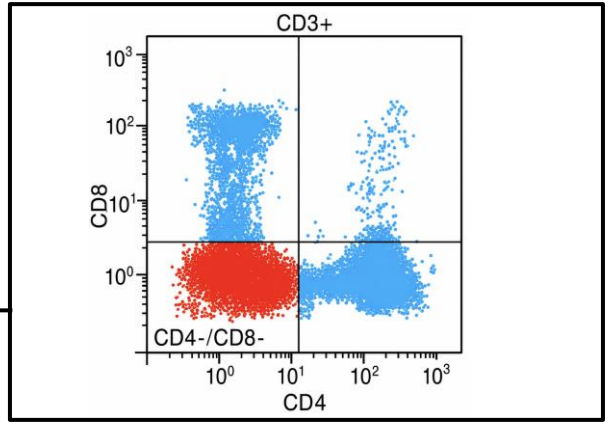
Accessory

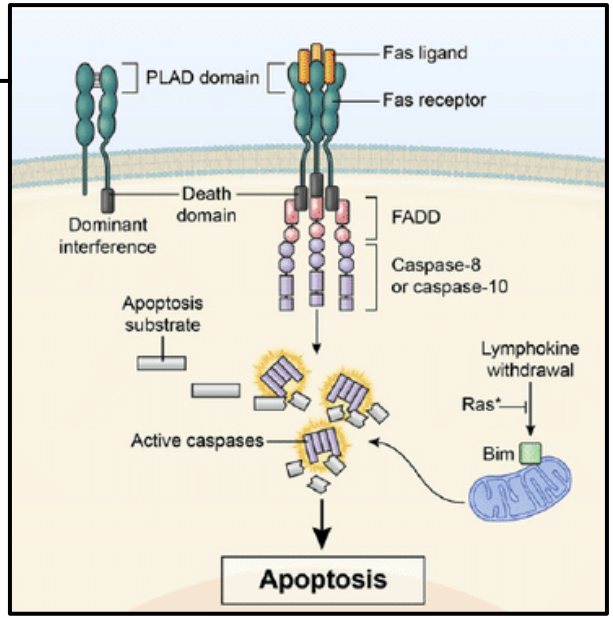
Primary

1. Defective lymphocyte apoptosis (in 2 separate assays)
2. Somatic or germline pathogenic mutation in *FAS*, *FASLG*, or *CASP10*

Secondary

1. Elevated plasma sFASL levels (>200 pg/mL) OR elevated plasma interleukin-10 levels (>20 pg/mL) OR elevated serum or plasma vitamin B_{12} levels (> 1500 ng/L) OR elevated plasma interleukin-18 levels > 500 pg/mL
2. Typical immunohistological findings as reviewed by an experienced hematopathologist
3. Autoimmune cytopenias (hemolytic anemia, thrombocytopenia, or neutropenia) AND elevated immunoglobulin G levels (polyclonal hypergammaglobulinemia)
4. Family history of a nonmalignant/noninfectious lymphoproliferation with or without autoimmunity



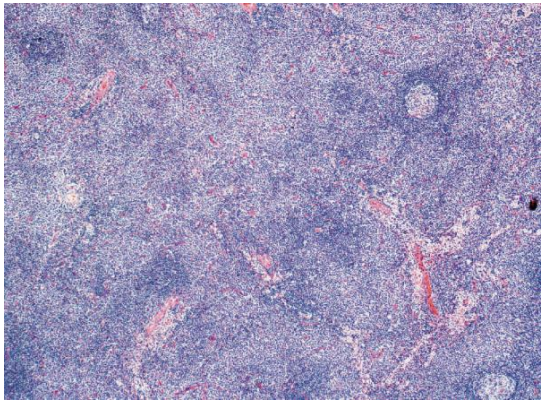


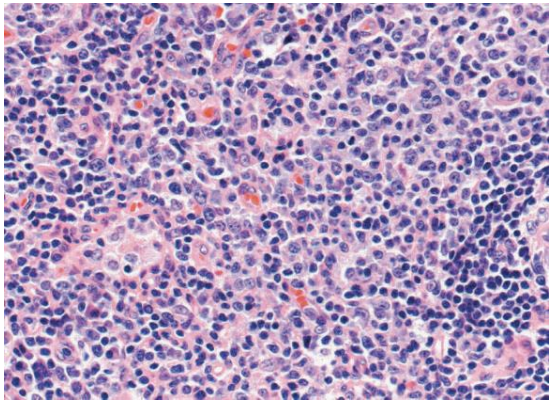
Blood. 2010;116(14):e35-40.

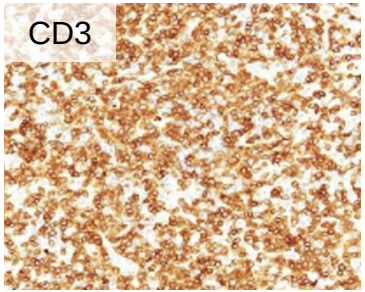
Lymphoid proliferations in ALPS and ALPS-like syndromes

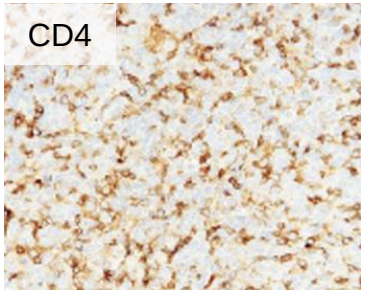
T-cells expansions

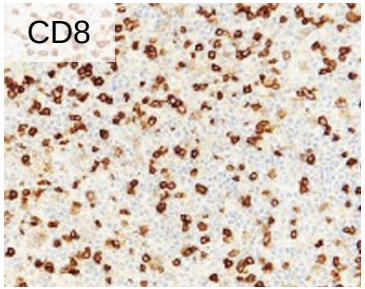
- Paracortical hyperplasia
- Increased DNTs









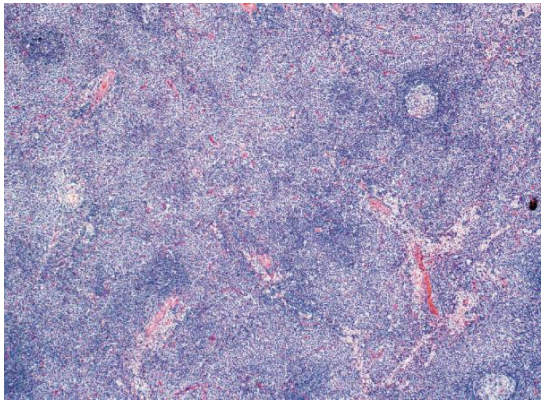


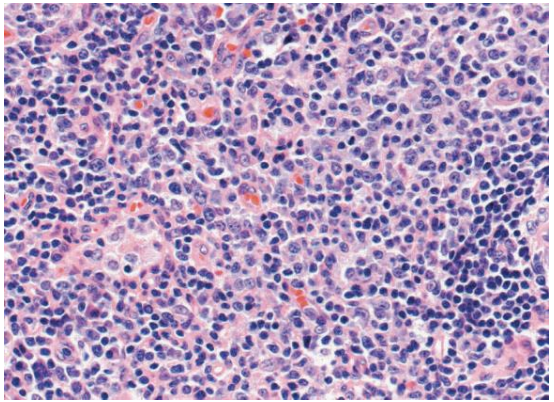
Gratzinger D et al. *Am J Clin Pathol*. 2017;147(2):204-216; van den Brand M et al. *Virchows Arch*. 2025;487(2):275-286; Lim MS et al. *Am J Pathol*. 1998;153(5):1541-1550

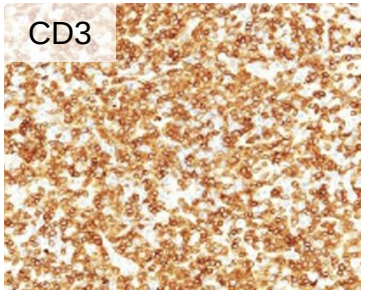
Lymphoid proliferations in ALPS and ALPS-like syndromes

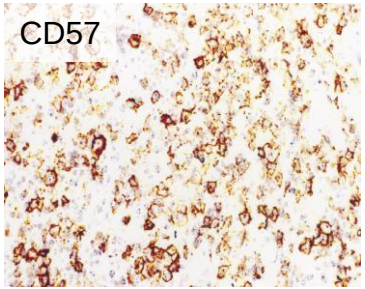
T-cells expansions

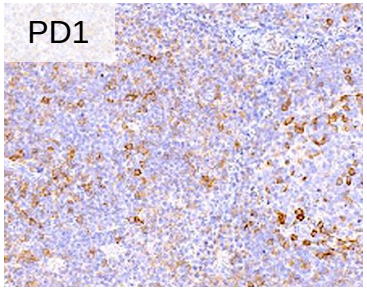
- Paracortical hyperplasia
- Increased DNTs
- Expansion of perifollicular CD57^{+} T-cells
- Increased perifollicular PD1^{+} T-cells





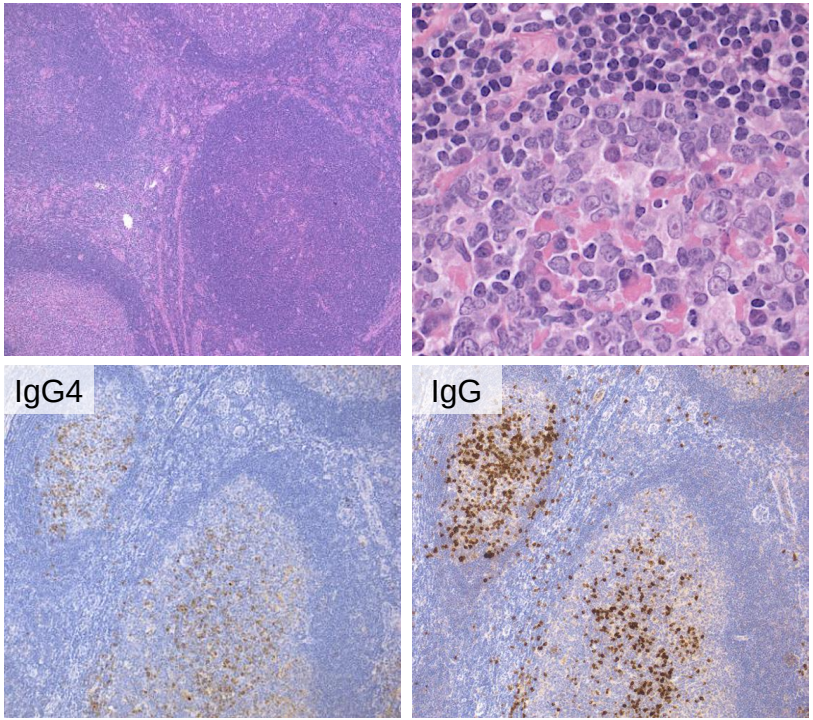






Gratzinger D et al. *Am J Clin Pathol*. 2017;147(2):204-216; van den Brand M et al. *Virchows Arch*. 2025;487(2):275-286; Lim MS et al. *Am J Pathol*. 1998;153(5):1541-1550

Lymphoid proliferations in ALPS and ALPS-like syndromes

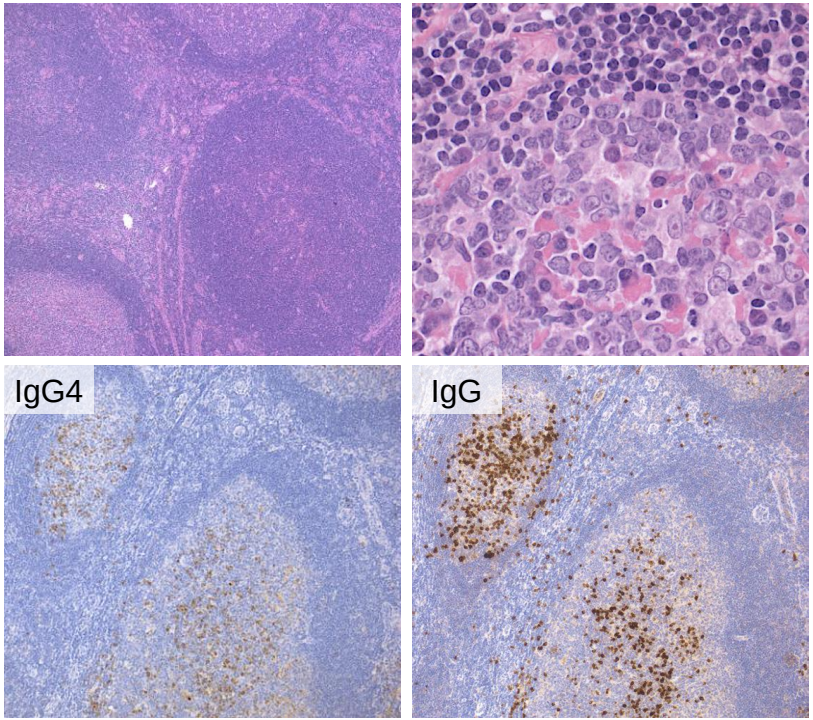


Mainardi C et al. *Pediatr Allergy Immunol*. 2020;31(3):332-336

B-cells and plasma cells proliferations

- Florid **follicular hyperplasia**
- Progressive transformation of GCs (**PTGC**)
- **Plasmacytosis** of GCs
- **IgG4-related lymphadenopathy**

Lymphoid proliferations in ALPS and ALPS-like syndromes



Mainardi C et al. *Pediatr Allergy Immunol*. 2020;31(3):332-336

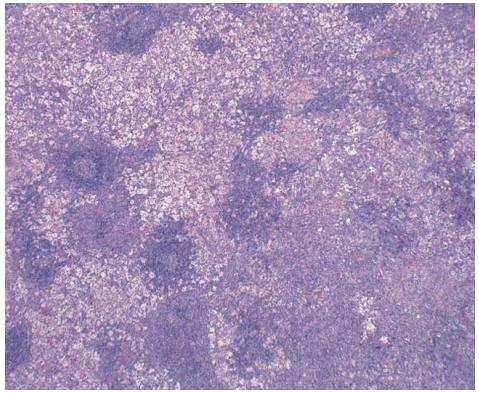
B-cells and plasma cells proliferations

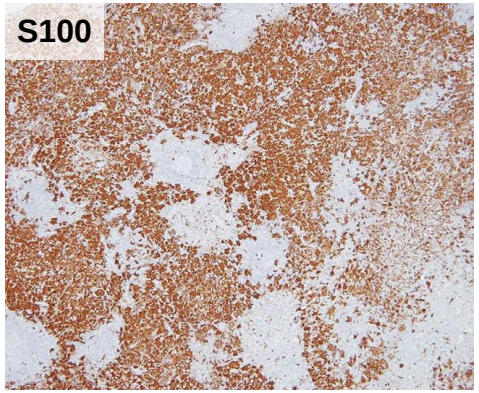
- Florid **follicular hyperplasia**
- Progressive transformation of GCs (**PTGC**)
- **Plasmacytosis** of GCs
- **IgG4-related lymphadenopathy**

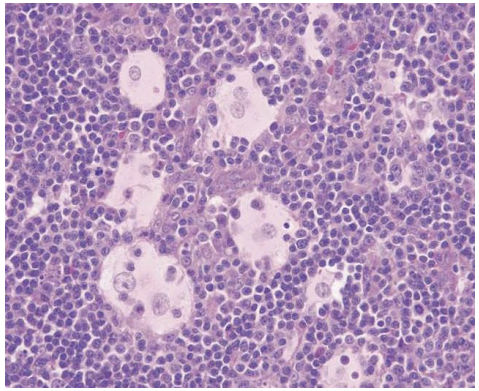
Increased risk for **Hodgkin** and **non-Hodgkin B-cell lymphomas**

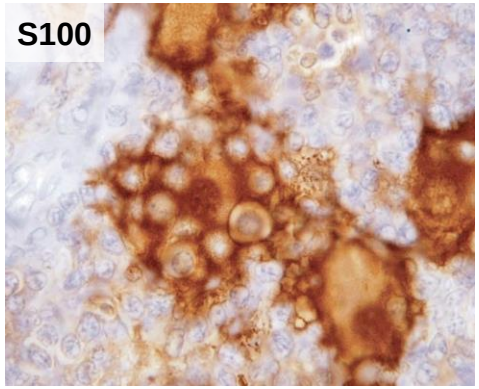
Rosai-Dorfman disease in ALPS and ALPS-like syndromes

- Features of RDD in **25-40%** of cases
- **Large** histiocytes with **evident nucleoli**
- Variable **emperipolesis**
- Positivity for **S100+** in histiocytes
- Numerous accompanying **plasma cells**









Maric I et al. *Am J Surg Pathol*. 2005;29(7):903-911

Conclusions

ALPS and **ALPS-like syndromes** can have **heterogeneous histological features**

Conclusions

ALPS and **ALPS-like syndromes** can have **heterogeneous histological features**

In the **IEI setting**, lymphoid expansions can **mimic lymphoma**

Conclusions

ALPS and **ALPS-like syndromes** can have **heterogeneous histological features**

In the **IEI setting**, lymphoid expansions can **mimic lymphoma**

Correct diagnoses rely on **clinical**, **histological** and **molecular integration**