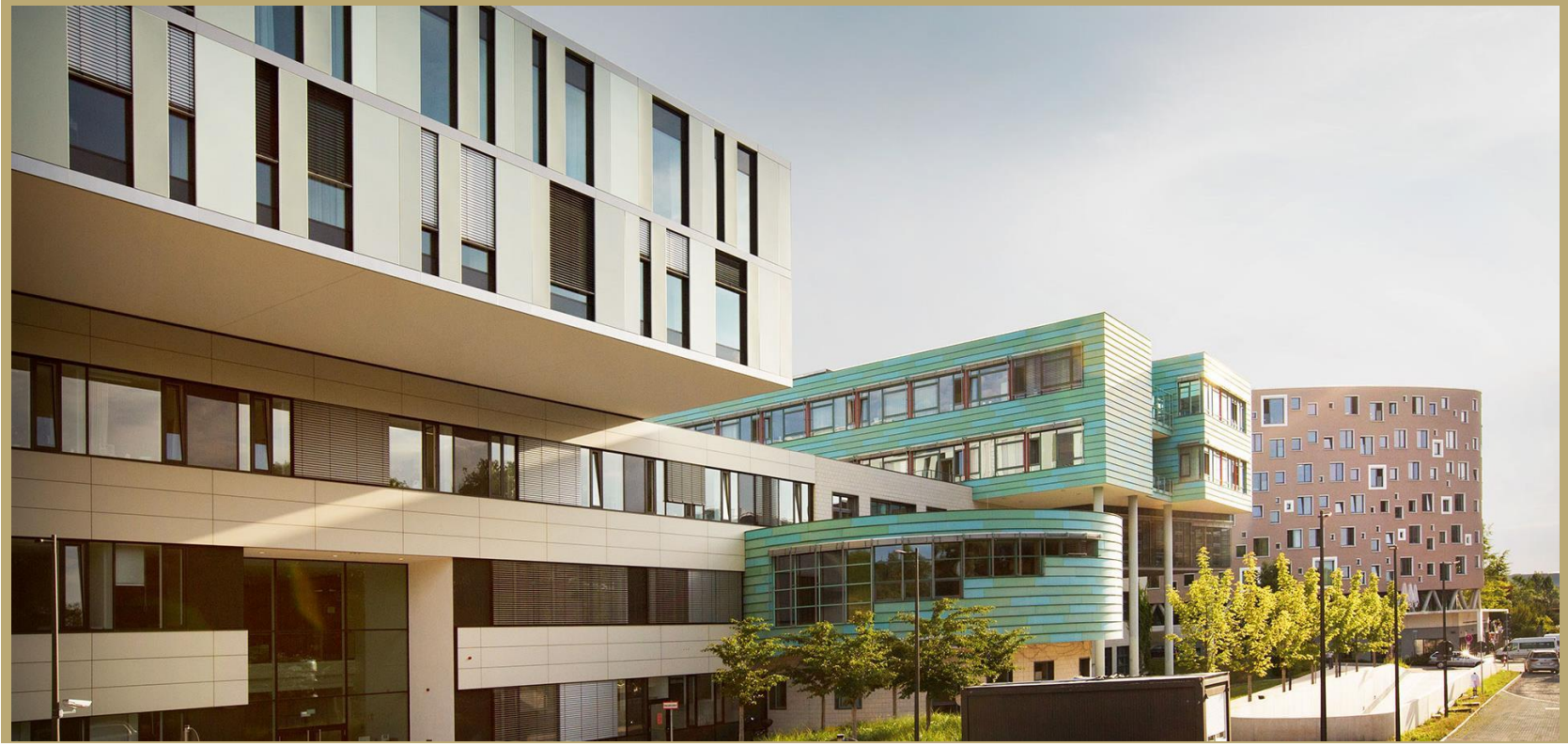
# EBV+ T and NK lymphoproliferative disorders



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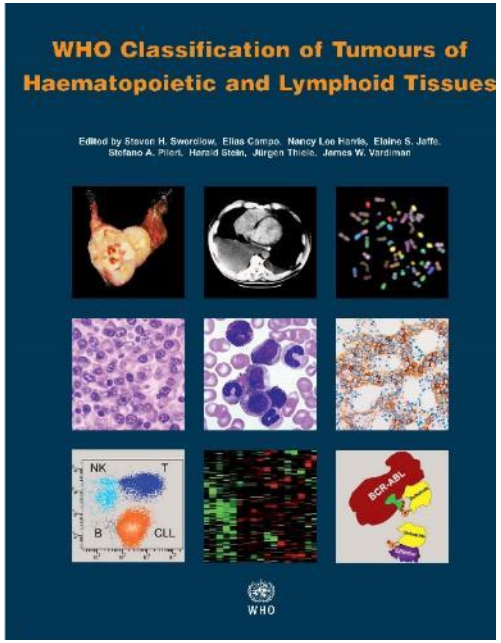
# EBV-associated T-and NK-cell LPD

| EBV-associated T-and NK-cell LPD<br>WHO 2017 | EBV-associated T and NK-cell LPD<br>International consensus classification 2022 |
|---|---|
| EBV+T and NK cell LPD in childhood | EBV+ T and NK cell LPD in childhood |
| ➢ Chronic active EBV infection<br>-Cutaneous form | |
| Hydroa vacciniforme-like LPD | ➢ Hydroa vacciniforme-like LPD<br>-*Classic form*: indolent, self-limited, more common in whites<br>-*Systemic form*: mild to severe, fever, lymphadenopathy, liver involvement, more common in Asia and Latin America |
| Severe mosquito bite allergy | ➢ Severe mosquito bite allergy |
| -Systemic form | ➢ Chronic active EBV disease, systemic<br>Only of T and NK cell type, B-cell cases excluded |
| ➢ Systemic EBV+T-cell lymphoma of childhood | ➢ Systemic EBV+T-cell lymphoma of childhood |
| Aggressive NK-cell leukemia | Aggressive NK-cell leukemia |
| Extranodal NK/T-cell lymphoma, nasal type | Extranodal NK/T-cell lymphoma, nasal type |
| *Primary EBV+ nodal T-cell and NK-cell lymphoma,* variant of PTCL, NOS | *Primary nodal EBV-positive T/NK cell lymphoma* |

*Quintanilla-Martinez L, Kimura H, Ko YH, Jaffe ES. Revised 2017 WHO classification*

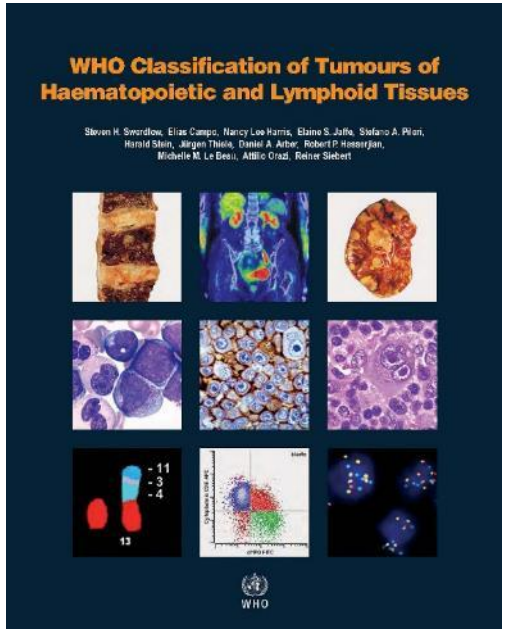
*Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow S, Blood 2022*

# Hydroa-vacciniforme LPD




2008

➡ Included as Hydroa vacciniforme-like lymphoma




2017

➡ Name changed to Hydroa vacciniforme-like LPD

➡ Name changed to Hydroa-vacciniforme LPD

2022 International Consensus Classification

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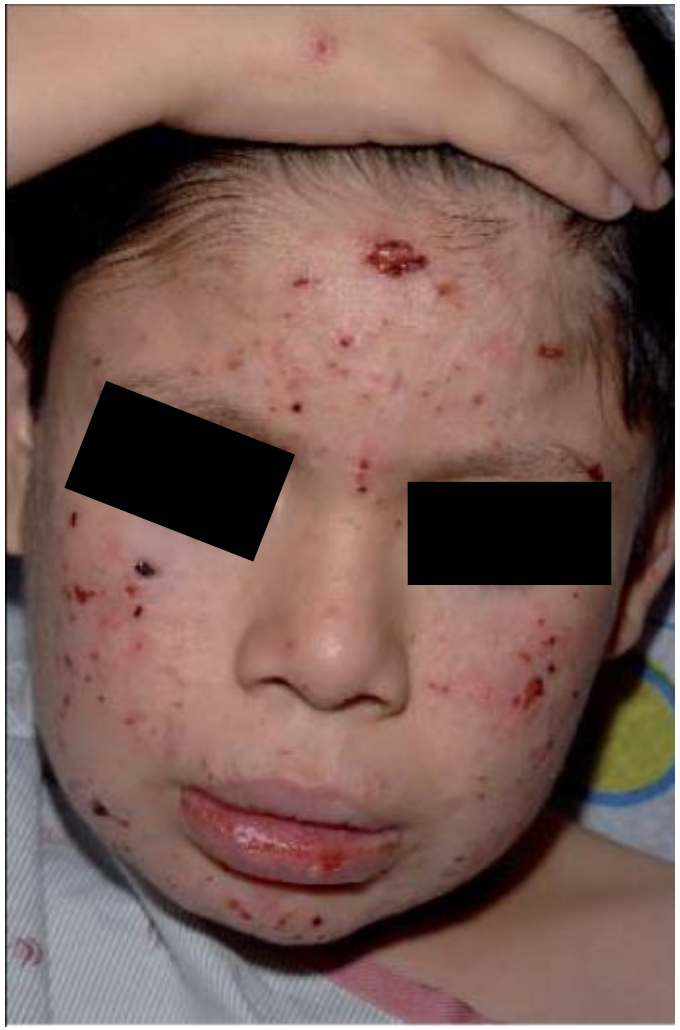
# Hydroa-vacciniforme LPD

- Definition:
  - Chronic EBV-positive LPD of childhood, associated with a risk of developing systemic lymphoma
  - Primarily cutaneous disorder with a broad spectrum of clinical aggressiveness.
  - Long clinical course.



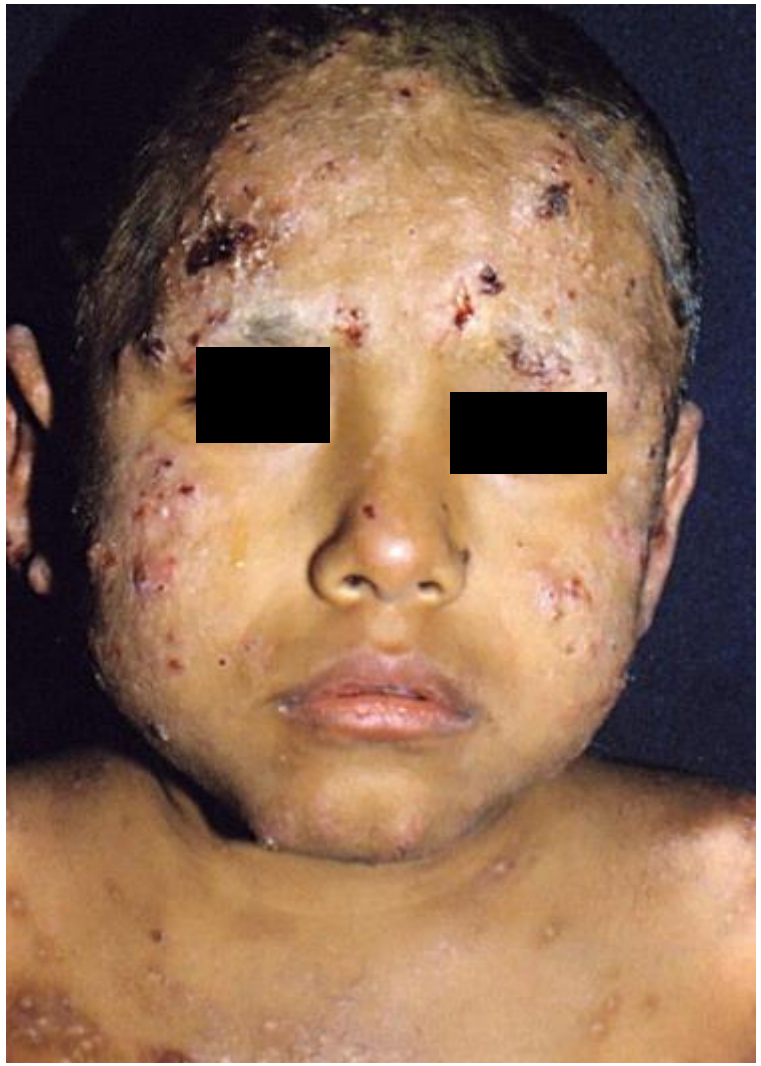
Synonyms:

- Edematous, scarring vasculitic panniculitis
- angiocentric cutaneous T-cell lymphoma
- Hydroa vacciniforme-like T-cell lymphoma
- Severe HV

*Quintanilla-Martinez L, Kimura H, Ko YH, Jaffe ES. Revised 2017 WHO classification*

# Hydroa-vacciniforme LPD

- Epidemiology:
  - Mainly children and adolescents from Asia and native Americans form Central and South America and Mexico
  - Median age at diagnosis is 8 years
  - Slightly predominates in boys
- Etiology:
  - Unknown
  - Defective cytotoxic immune response to EBV-infection (genetic predisposition)
- Treatment:
  - A conservative approach is recommended
    - No response to conventional chemotherapy
  - Hematopoetic stem cell transplantation in advanced cases

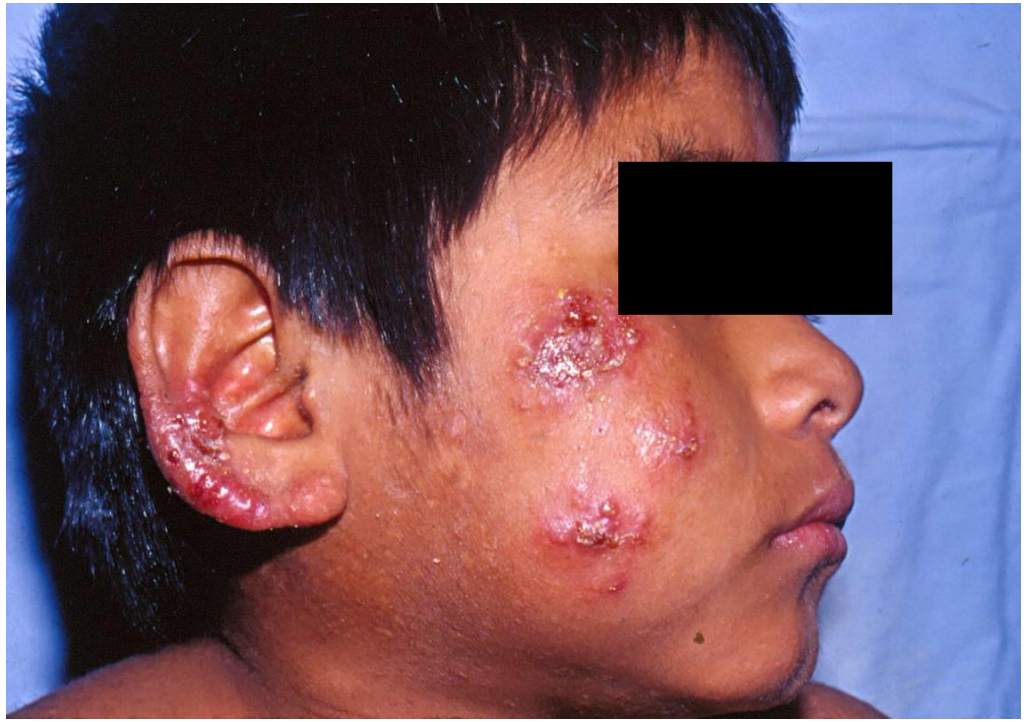


*Quintanilla-Martinez L, Kimura H, Ko YH, Jaffe ES. Revised 2017 WHO classification*

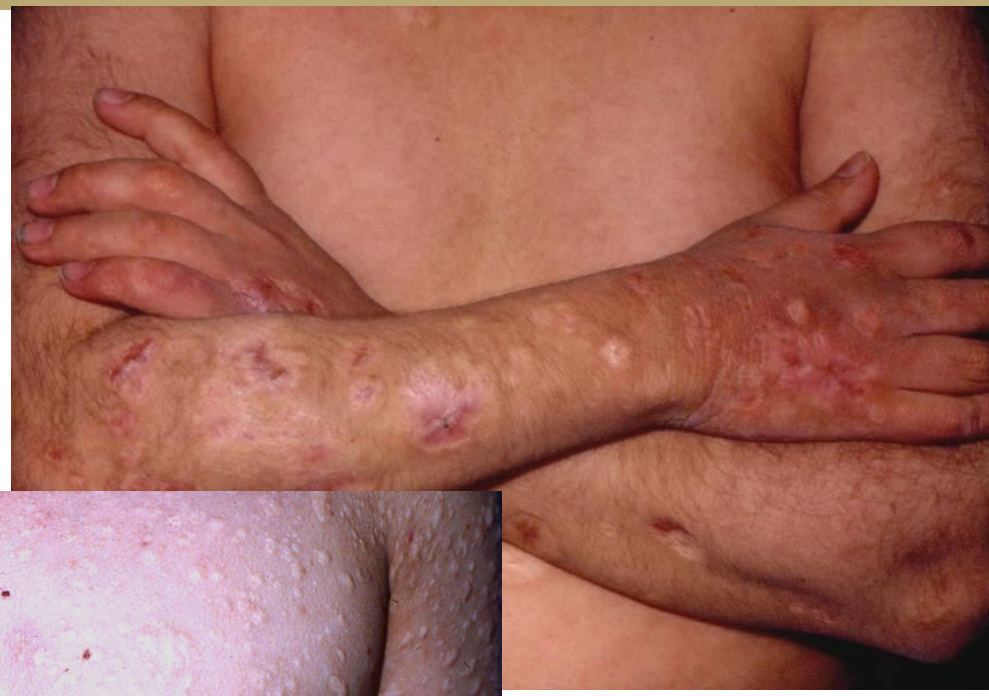
*Quintanilla-Martinez L, et al Blood 2013;122:3101*

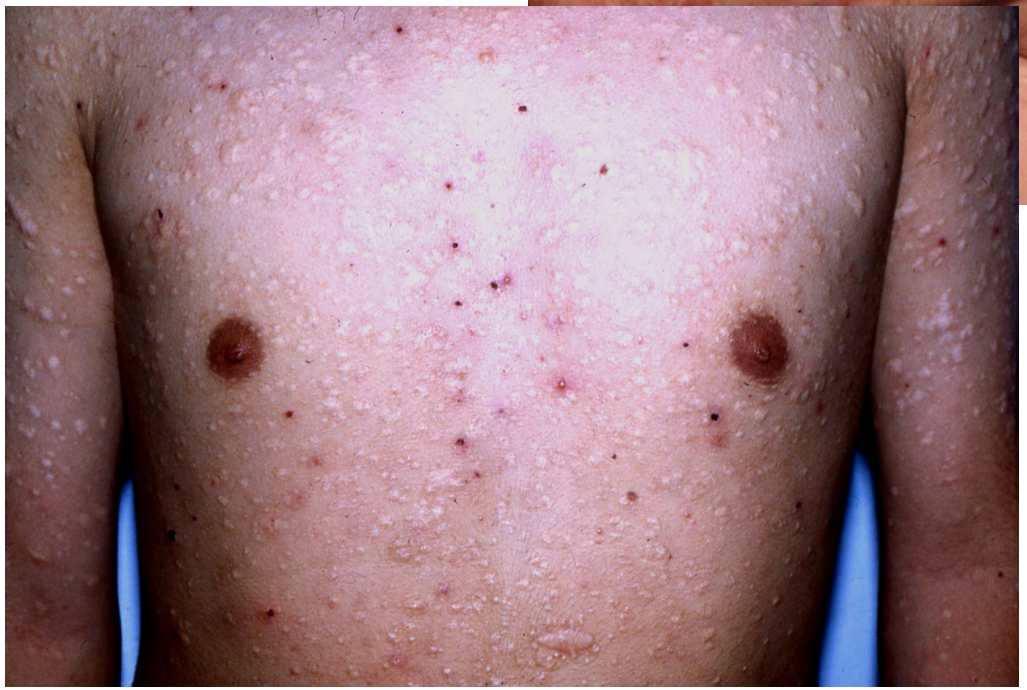
# Hydroa-vacciniforme LPD

Clinical features: Characterized by papulovesicular eruptions that generally proceeds to ulceration and scarring



8 year-old boy





*Quintanilla-Martinez L, et al Blood 2013;122:3101*

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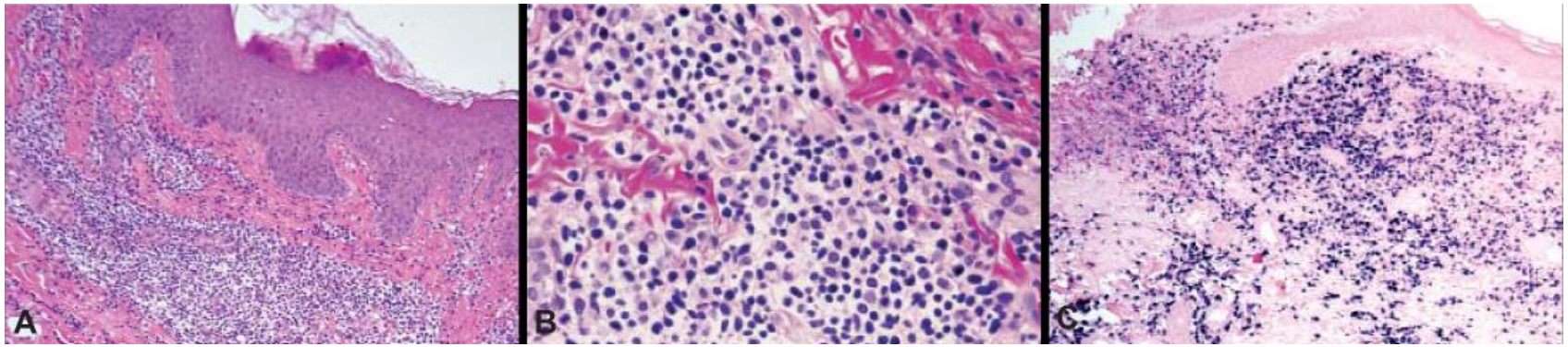
# Hydroa-vacciniforme LPD

## ➢ Morphology:

- Infiltrating cells are small to medium in size without significant atypia
- Infiltration of the epidermis to the subcutis
- Angiocentricity and angioinvasion
- Usually CD8+

## Prognosis:

- The clinical course is variable,
- recurrent skin lesions up to 10-15 years,
- progression to systemic disease can occur

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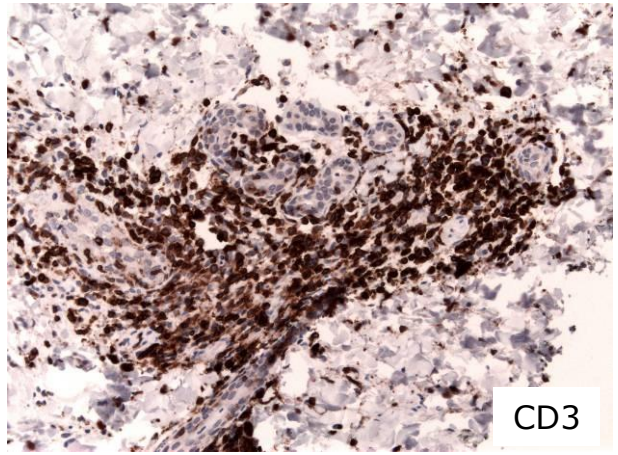
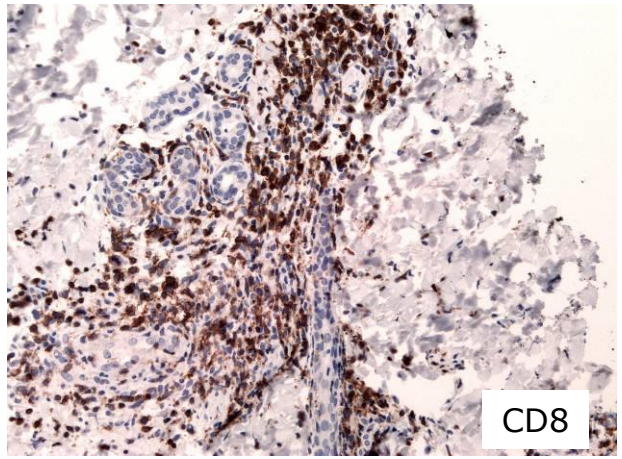
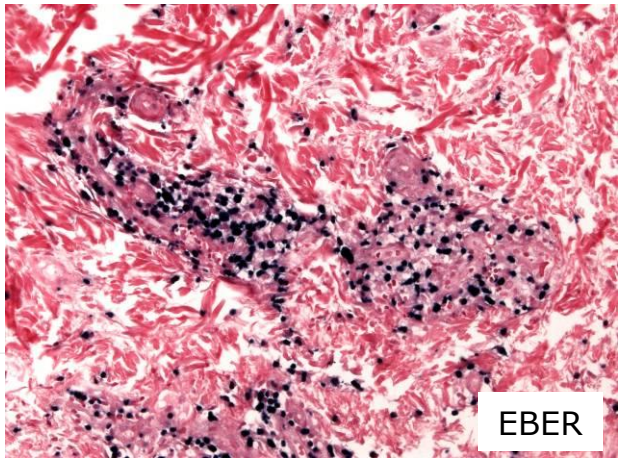
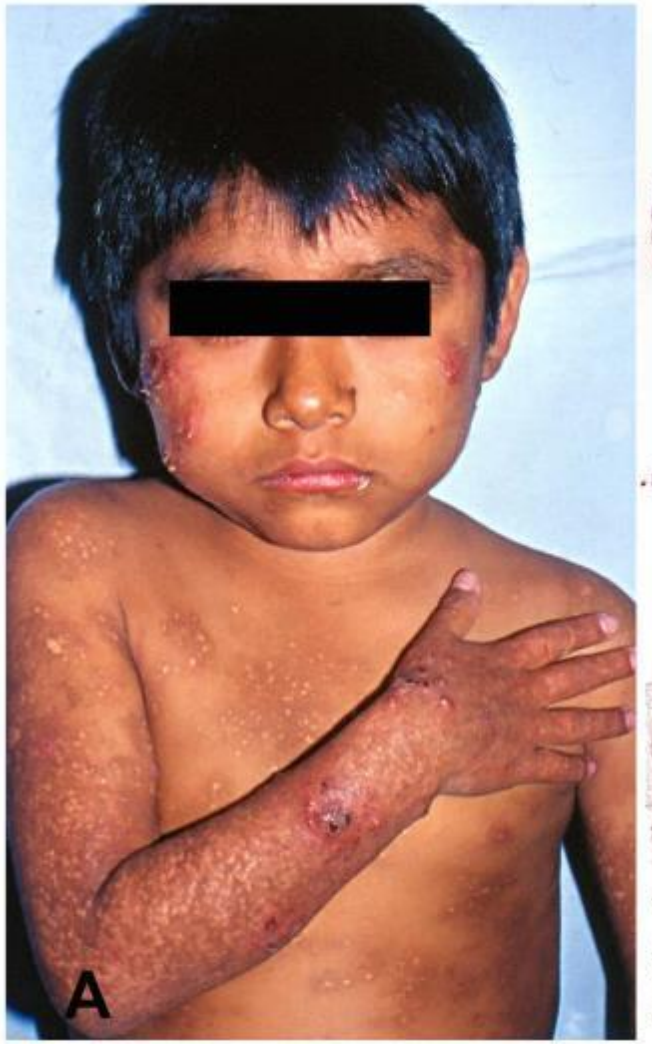
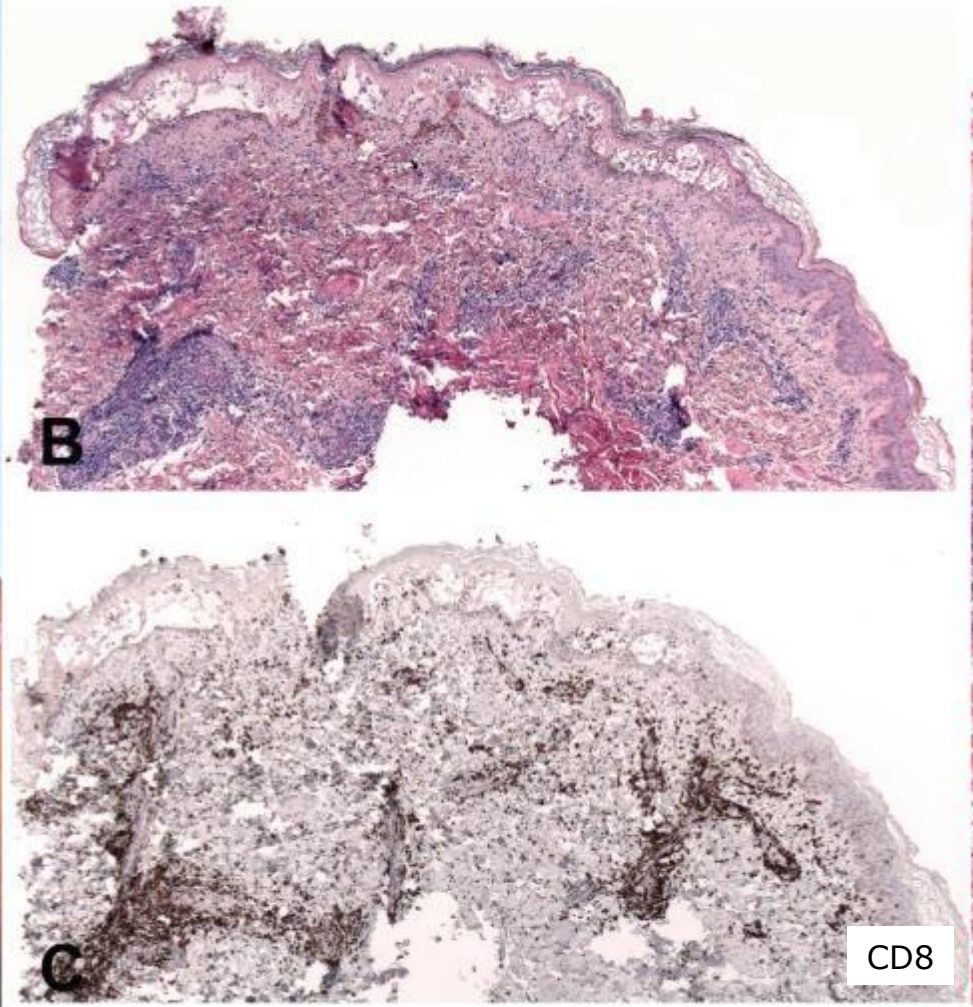


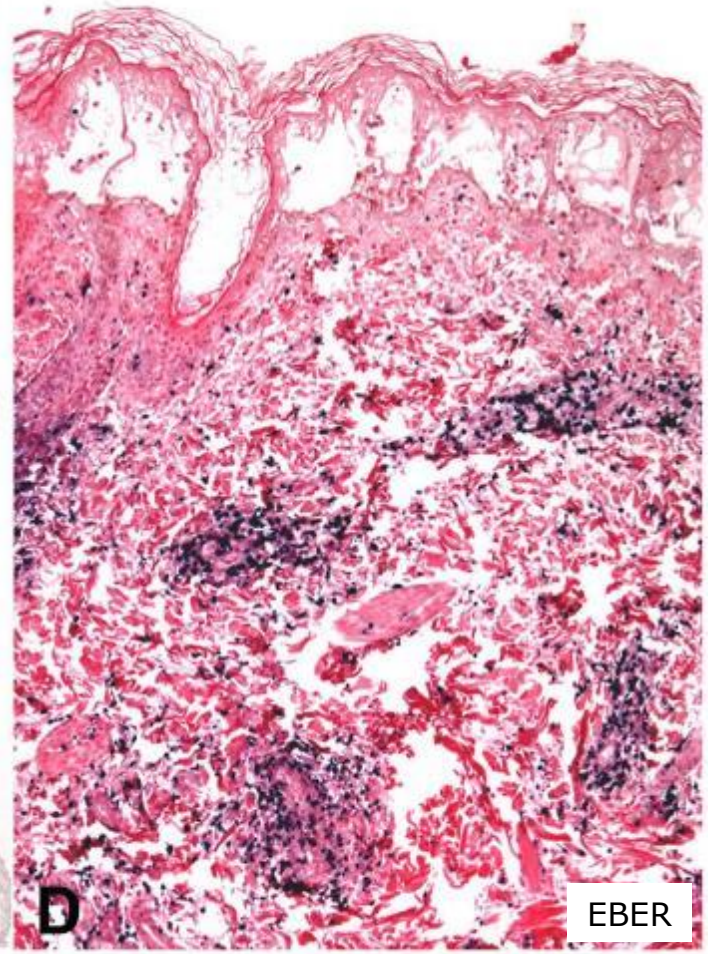



# Hydroa-vacciniforme LPD




*Dojcinov SD, Fend F, Quintanilla-Martinez L. Pathogens 2018*

*Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow S, Blood 2022*

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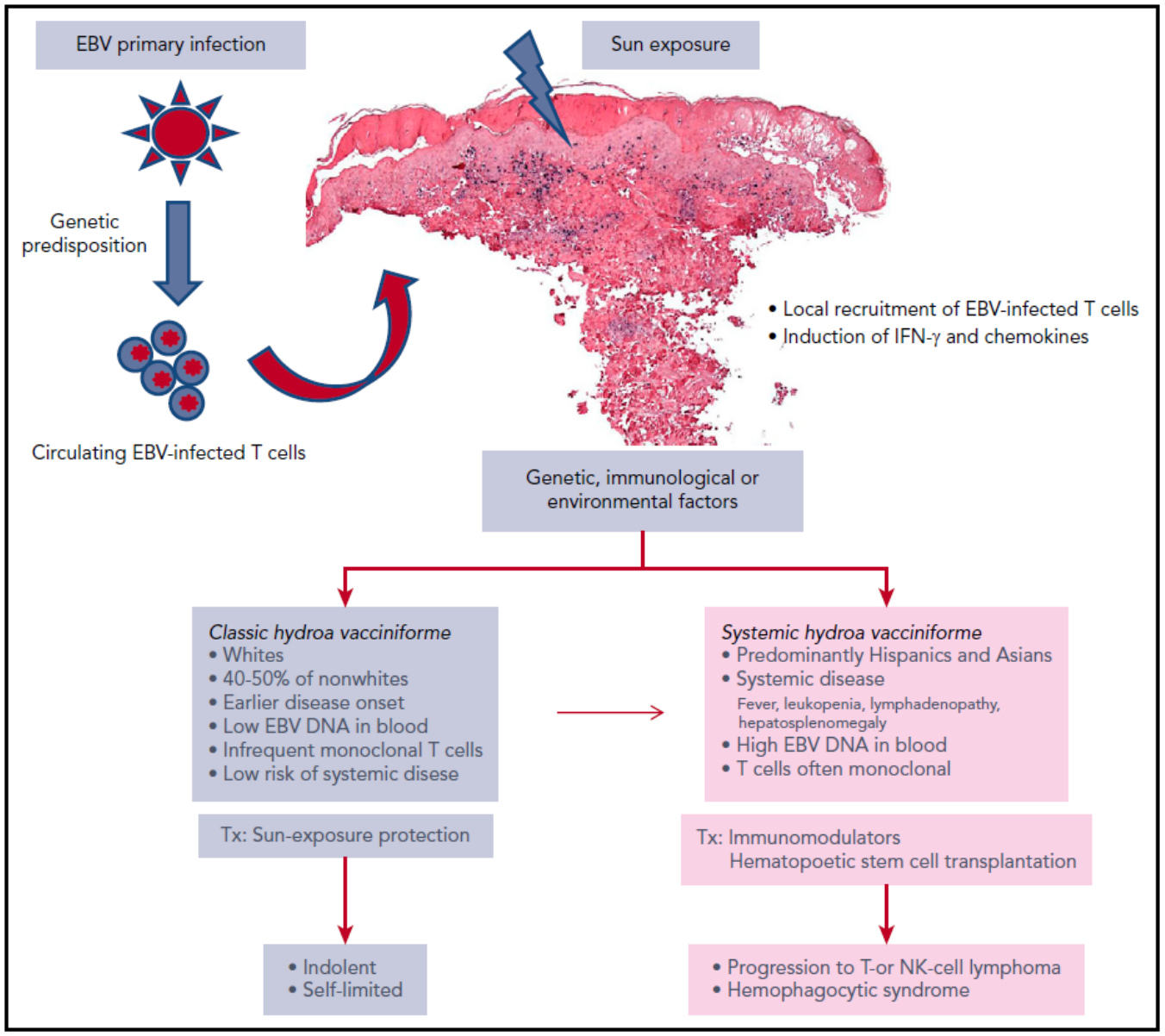
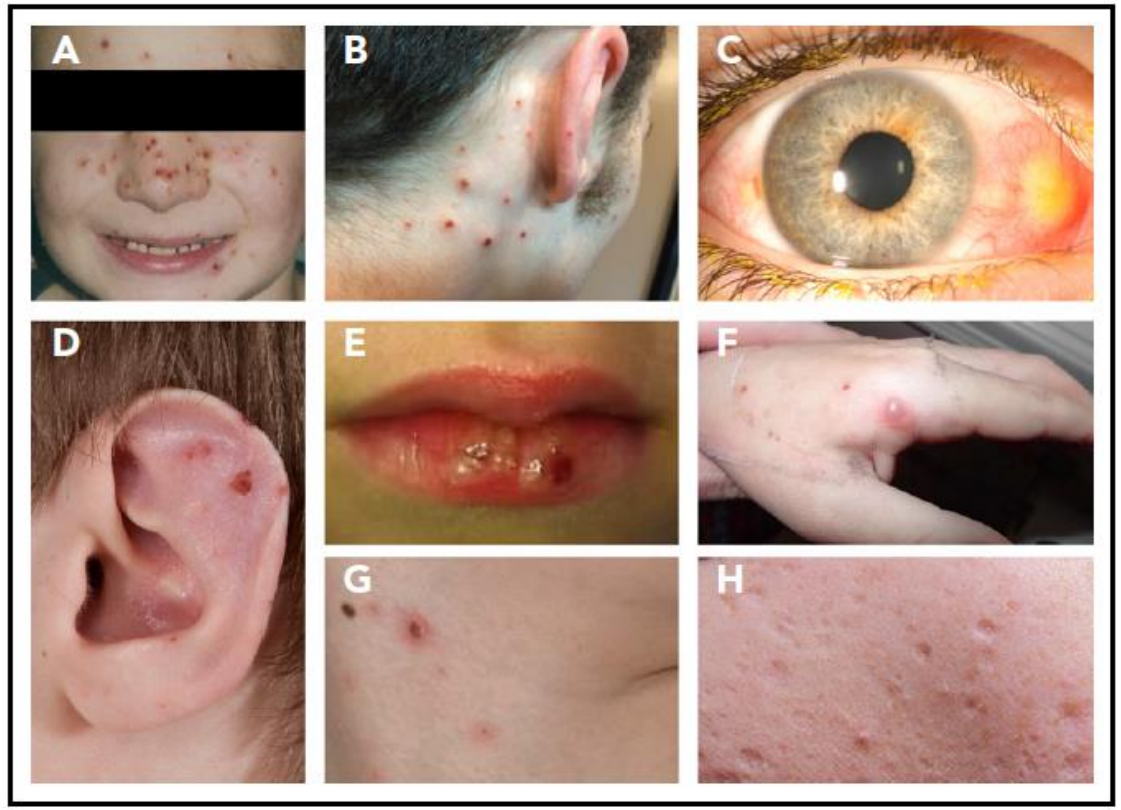
# Hydroa-vacciniforme-like LPD




*Cohen JI., Blood 2019;133:2753*

*Quintanilla-Martinez et al., Blood 2019;133:2735*

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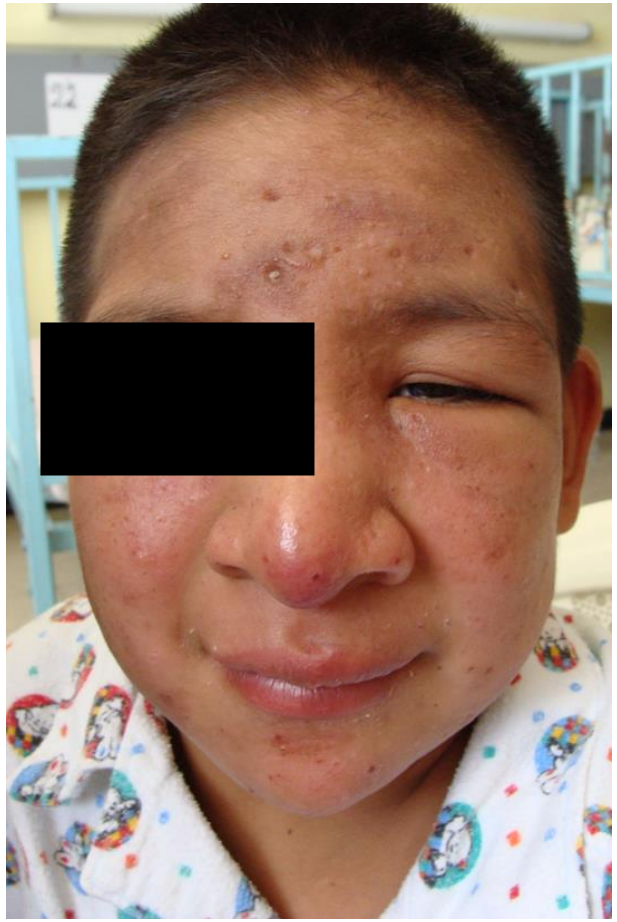
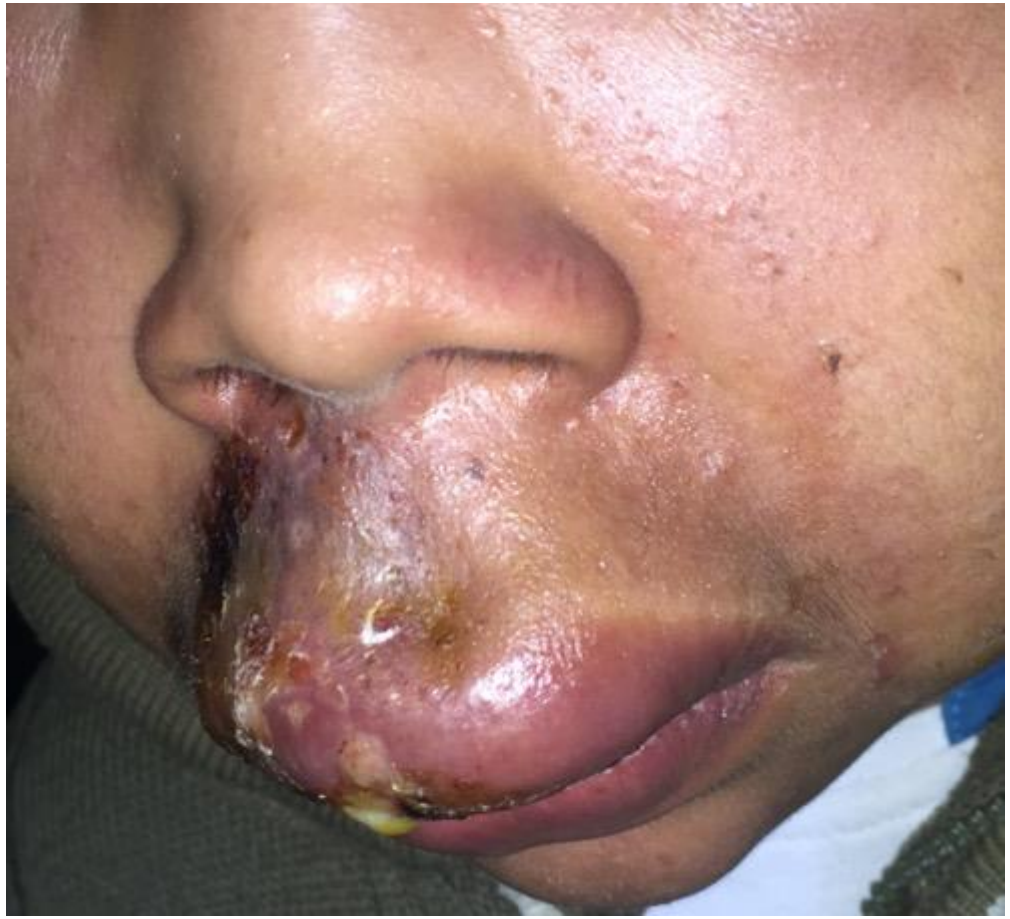
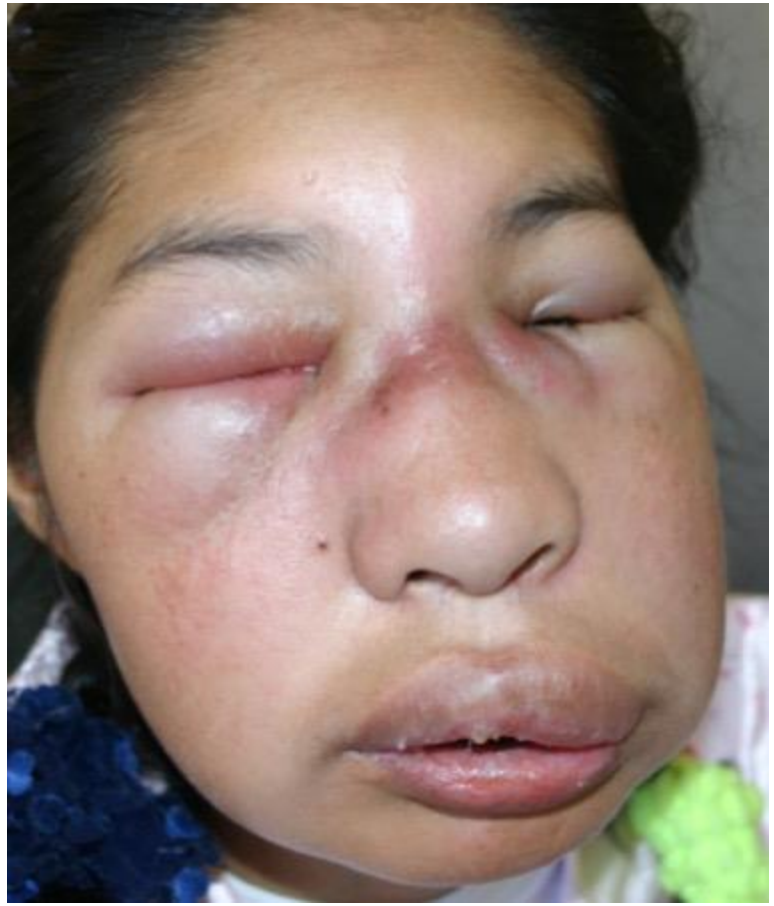
# Hydroa-vacciniforme LPD vs CAEBV disease







9 year-old boy

*Sanguenza M, Quintanilla-Martinez L, WHO 2021 pediatric neoplasias*

*Campo E, Jaffe ES, Cook JR, Quintanilla-Martinez L, Swerdlow S, Blood 2022*

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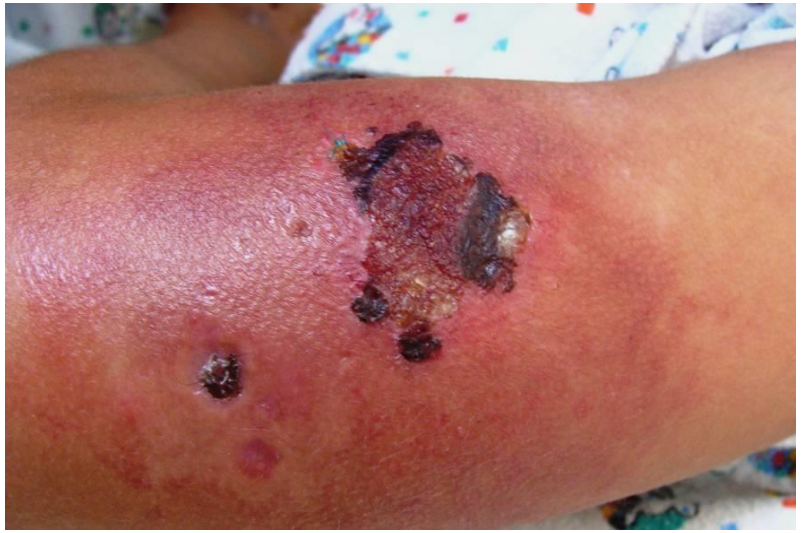
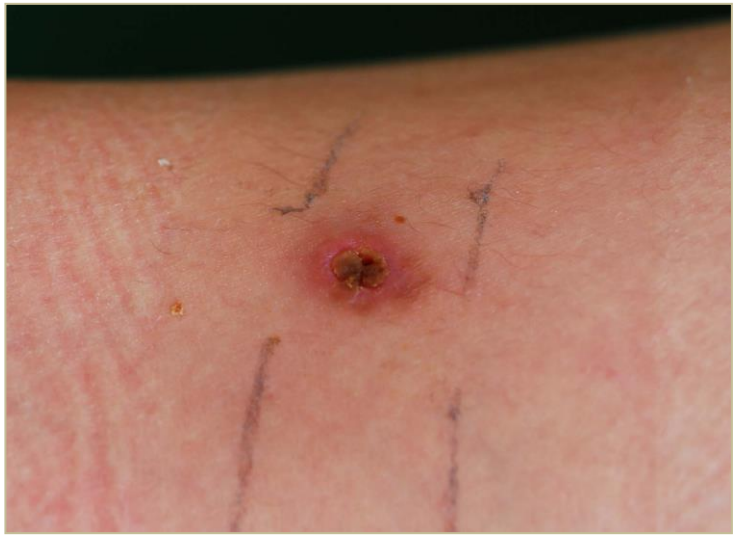
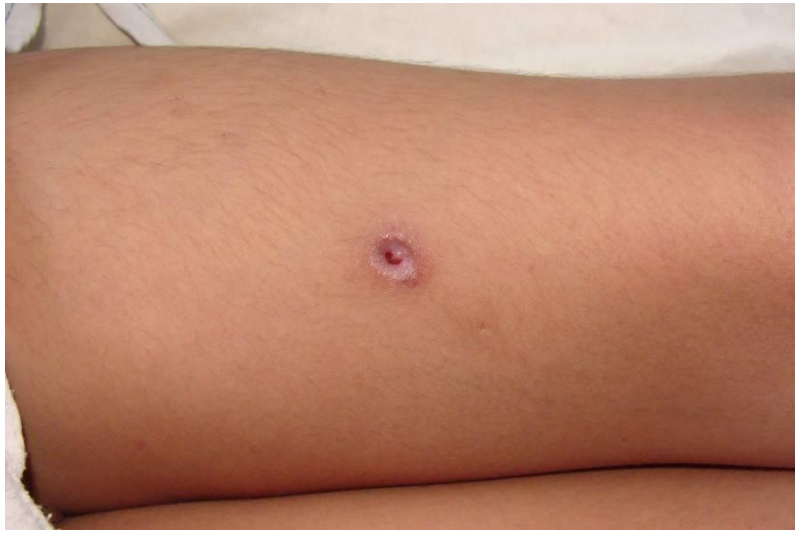
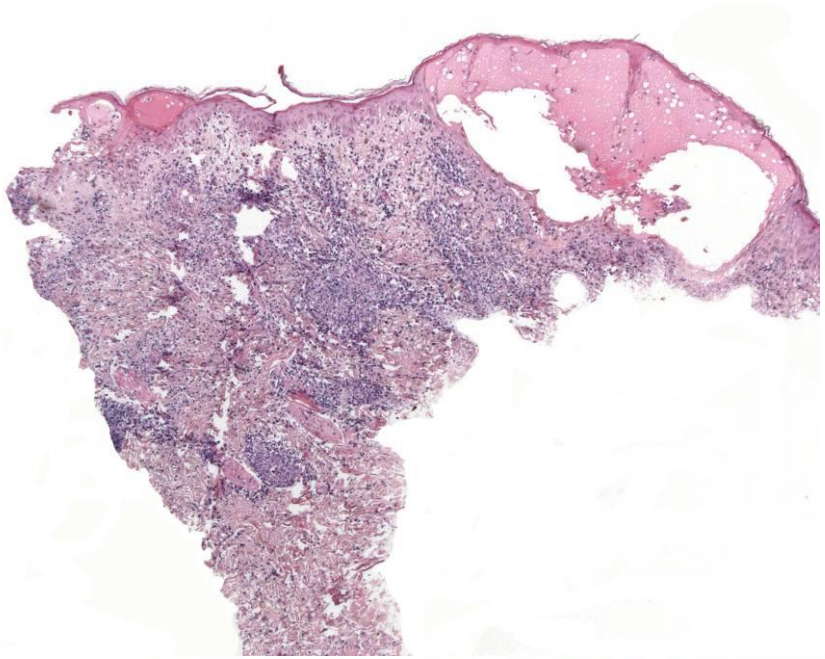
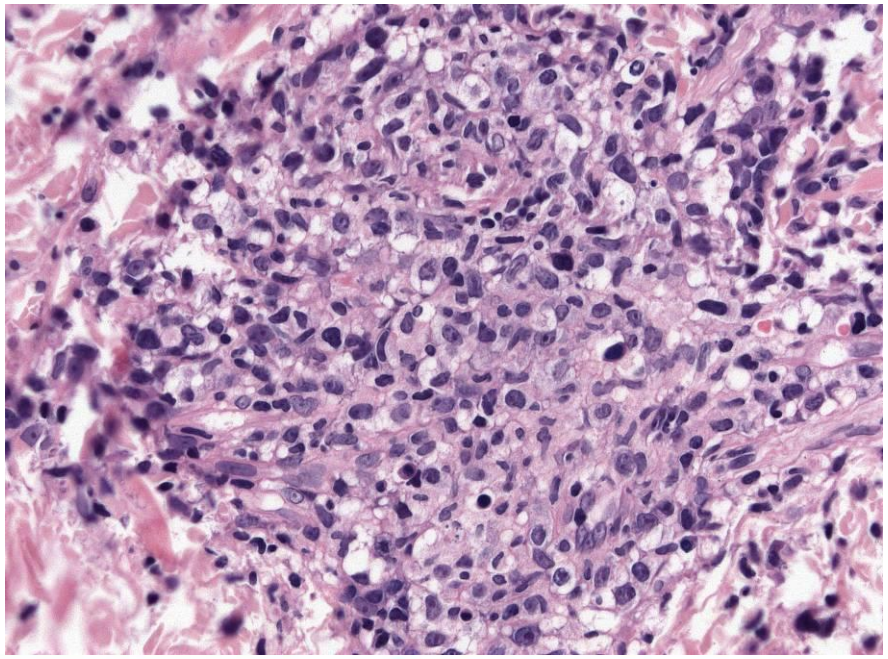
# Severe mosquito bite

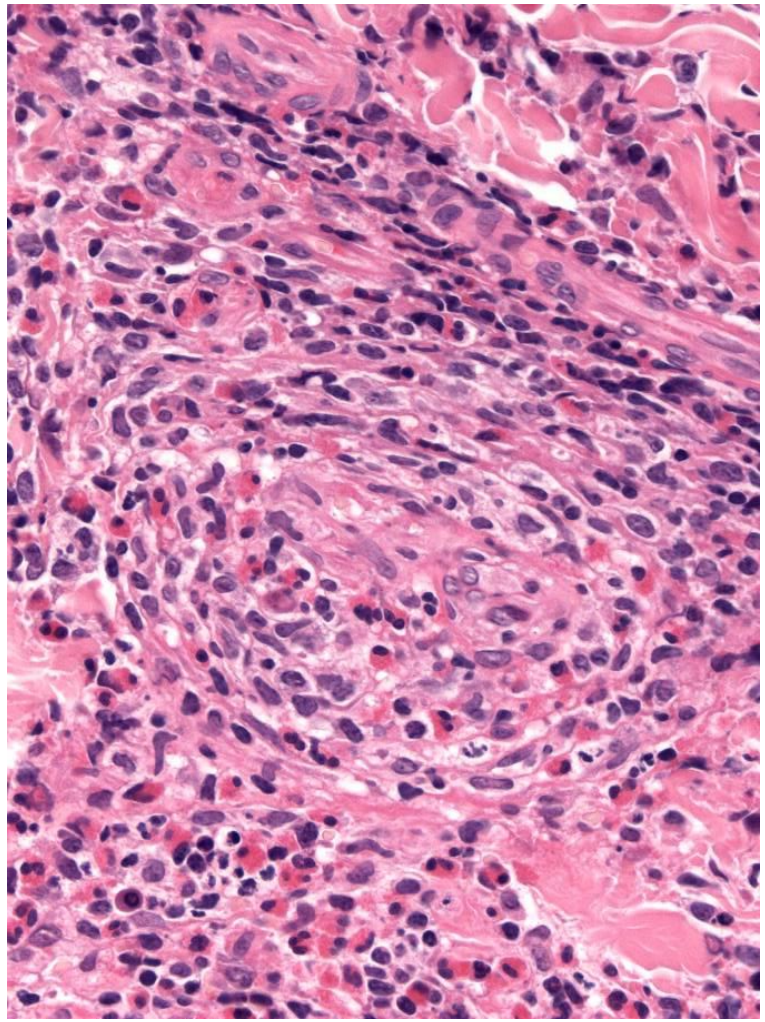




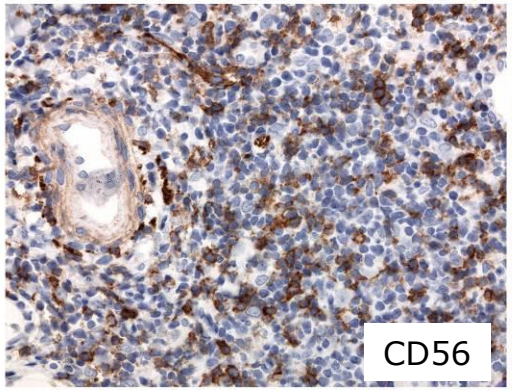
- Described mainly in Japan
- EBV+NK-cell proliferation characterized by fever after mosquito bites followed by edema, ulceration, skin necrosis and deep scarring without the characteristic lesions of HV or the general symptoms of CAEBV
- Risk to develop a NK/T-cell lymphoma
- NK–cell lymphocytosis, elevated IgE in serum and detection of EBV DNA in Blood.

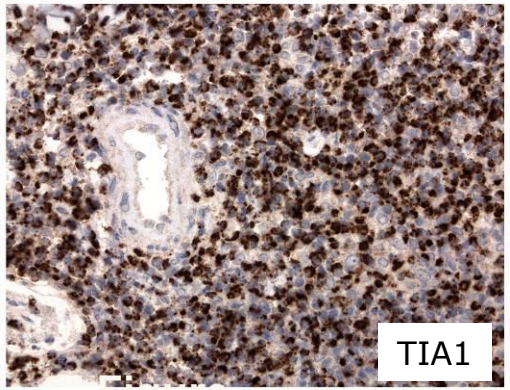
# Severe mosquqito bite

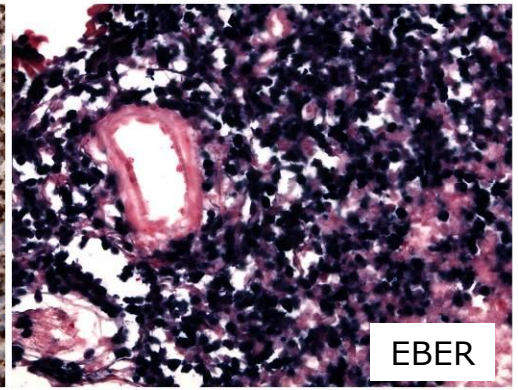




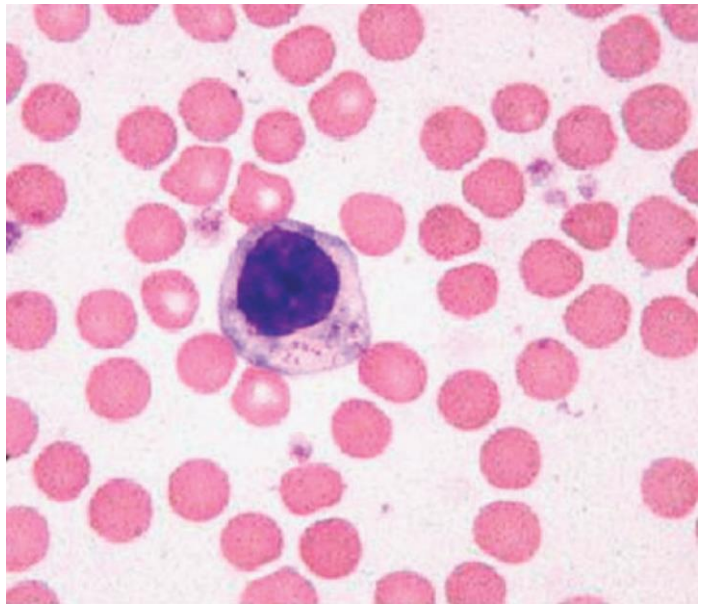


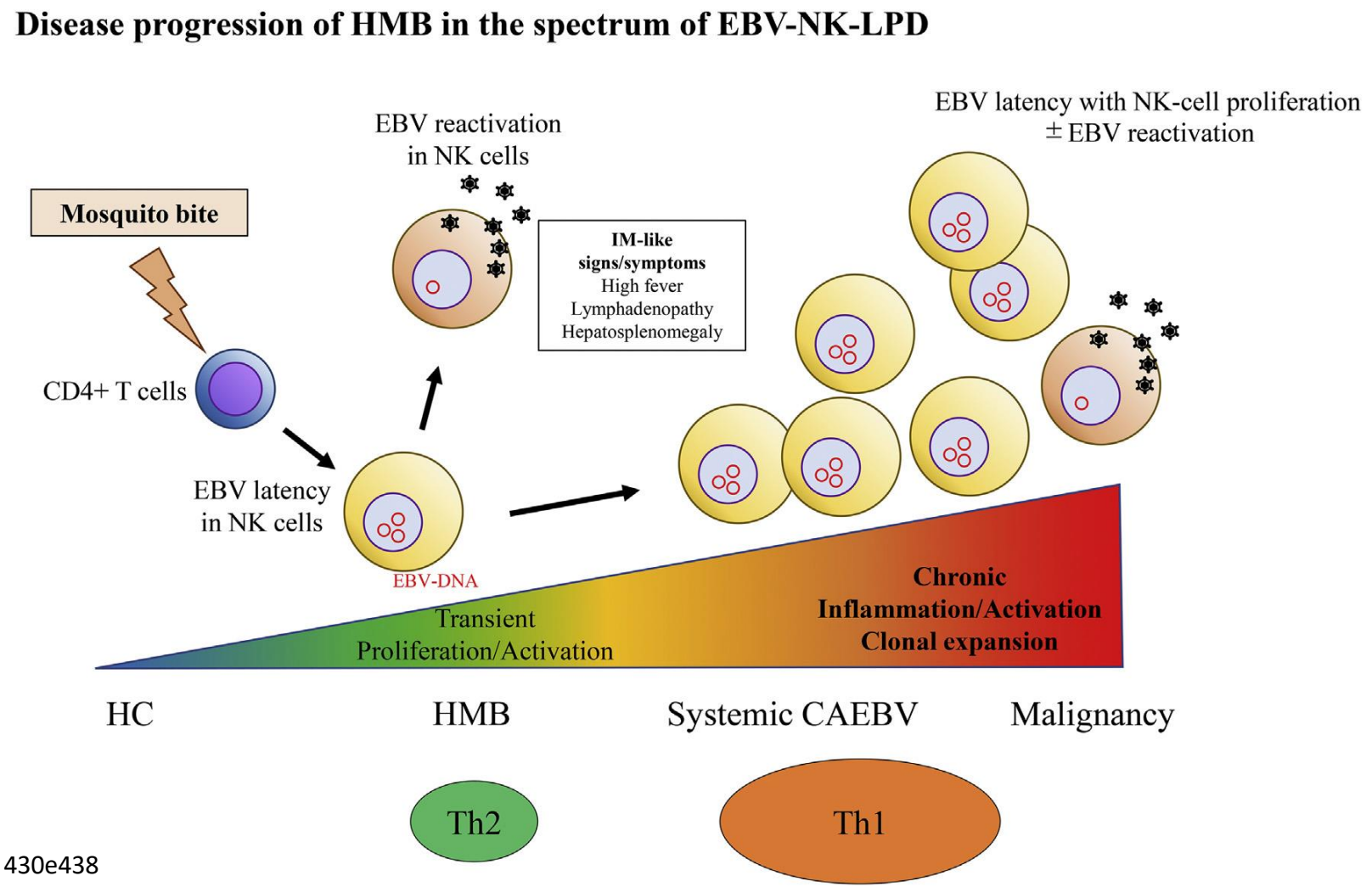


# Severe mosquqito bite






M. Yamada et al. / Allergology International 70 (2021) 430e438

# Chronic active EBV Infection (CAEBV)

**Clinical:** Intermittent fever, lymphadenopathy and hepatosplenomegaly for 6 months
Affects mostly children (<15 year)

**Hematologic:** A disorder of B-cells
Pancytopenia or lymphocytosis, polyclonal gammopathy

**Virological:** Elevated antibody titers against EBV. (VCA IgG:>5 120; EA IgG > 640) and/or detection of EBV genomes in affected tissues.

**Other:** Chronic illness, which cannot be explained by other known disease process.

*Straus SE. J Infect Dis 1998; 157:405-12*
*Okano M, Purtillo DT, et. Al. Clin Microbiol Review 1991*

# CAEBV infection – revised criteria

- Chronic EBV infection of T-, NK- or B cells
- Clinically presents with fever, lymphadenopathy and splenomegaly (HPS, DIC, hepatic failure, gastric perforation, CNS complications, myocarditis and interstitial pneumonitis)
- Symptoms most be at least 3 months
- Increased EBV DNA in peripheral blood ($10^4$-$10^7$ EBV genomes in $10^6$ cells)
- EBV-EBER postive cells in tissue
- Not known immunodeficiency

NIH 2008

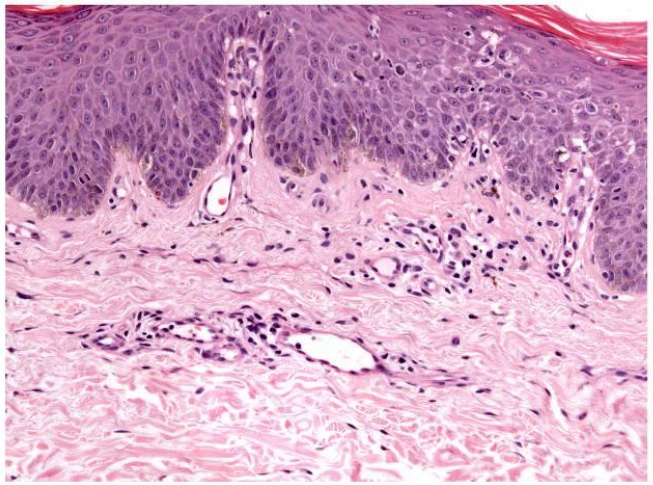
*Kimura H, Blood 2001;98:280-286*
*Cohen JI, et al 2009, 20:1472*

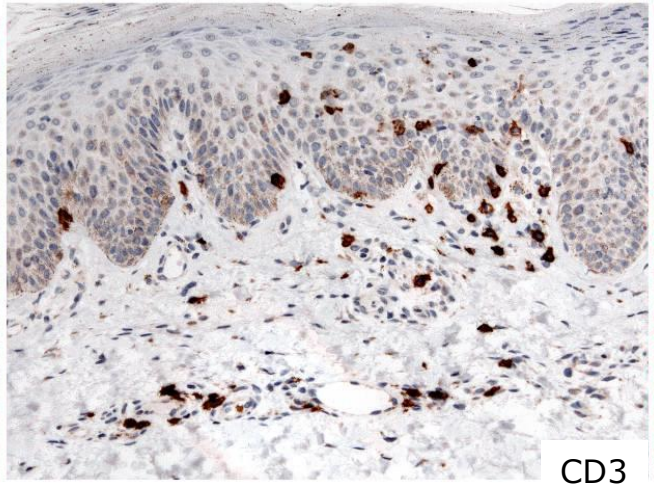
# Chronic active EBV disease

- **Definition:**
  - Systemic, EBV disorder (polyclonal, oligoclonal or monoclonal) with IM-like symptoms
  - The infected cells are T and NK-cell type. B-cell type is excluded
  - Strong racial predisposition
  - Different degrees of clinical severity depending on the host immune response and the EBV viral load
- **Molecular findings:**
  - TCR monoclonal, oligoclonal or polyclonal
- **Treatment**
  - The only proven effective treatment is hematopoietic stem cell transplantation
- **Prognosis:**
  - Patients succumb to opportunistic infections, hemophagocytosis, multiorgan failure or EBV-positive lymphoma

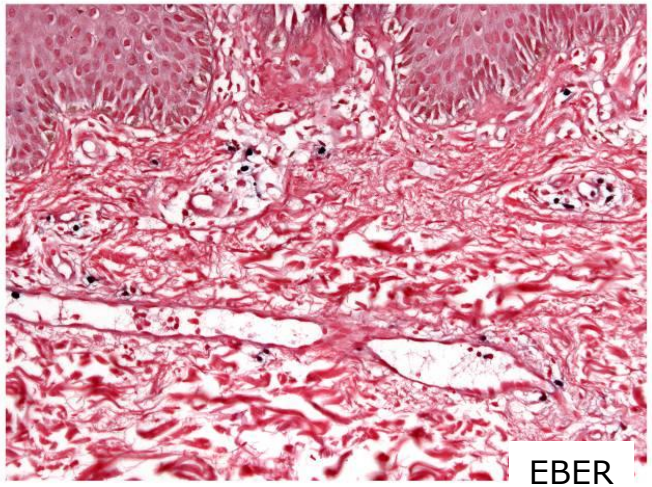
# Chronic active EBV disease

- 50% present with IM-like symptoms
- Skin rash (26%), rarely HV type lesions
- Uveitis (5%)
- Coronary artery aneurism (9%)
- Hepatitis, hepatic failure (15%)
- Interstitial pneumonia (5%)
- CNS involvement (7%)
- Gastrointestinal perforation (11%)
- Myocarditis (4%)



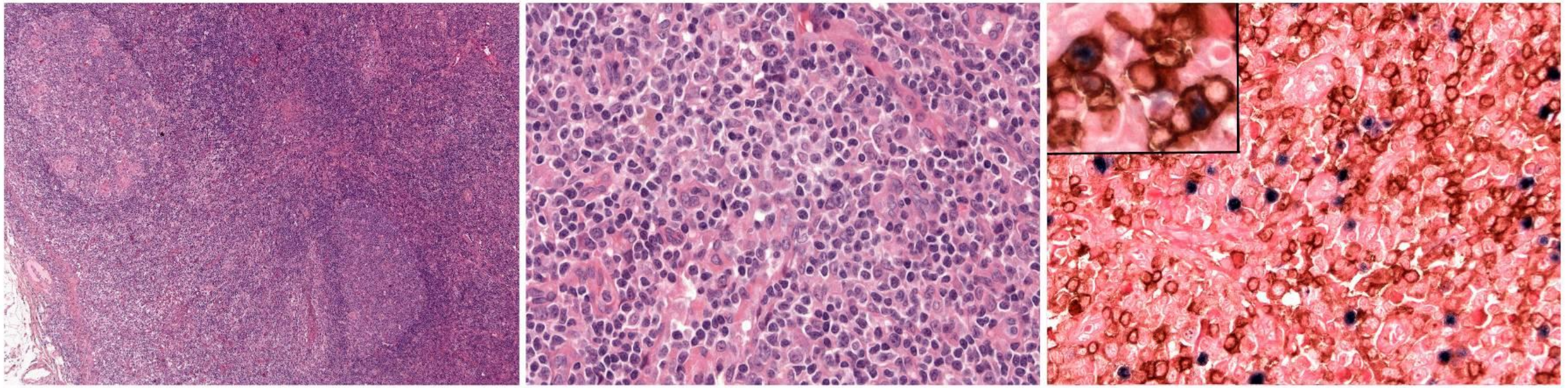


CD3



EBER

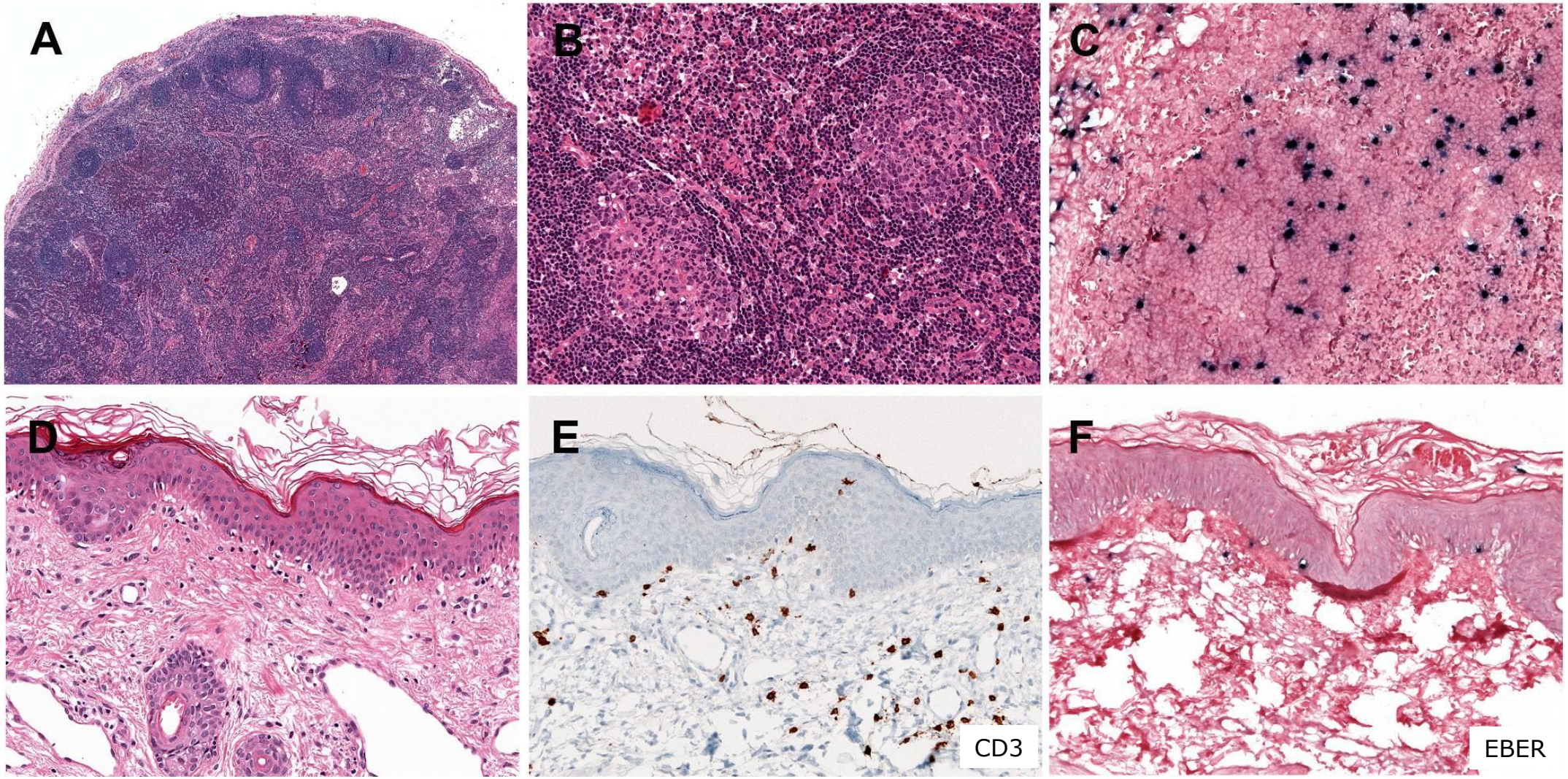
# Chronic active EBV disease



CD4/EBER

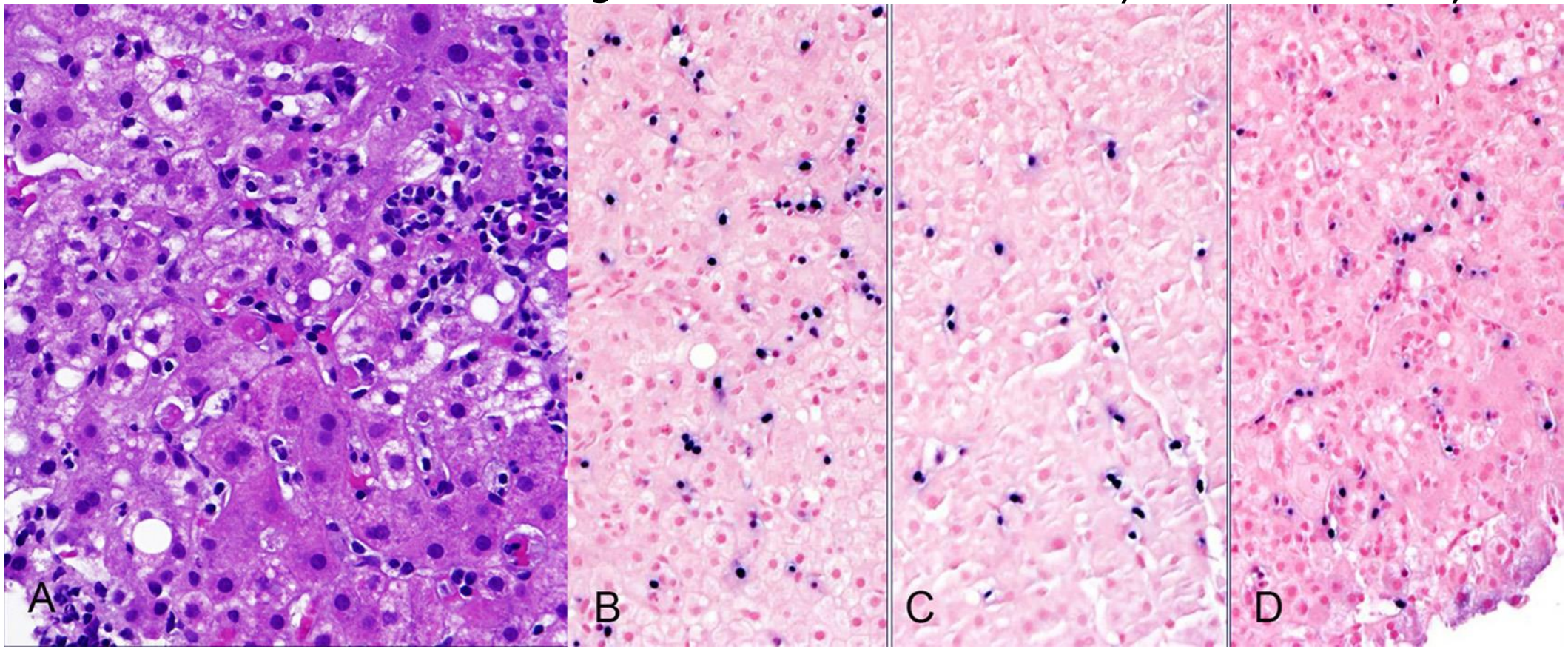
- The lymph nodes show variable morphology
  - Paracortical hyperplasia
  - Follicular hyperplasia
  - Focal necrosis
  - Small epithelioid granulomas

# Chronic active EBV disease



# Chronic active EBV disease

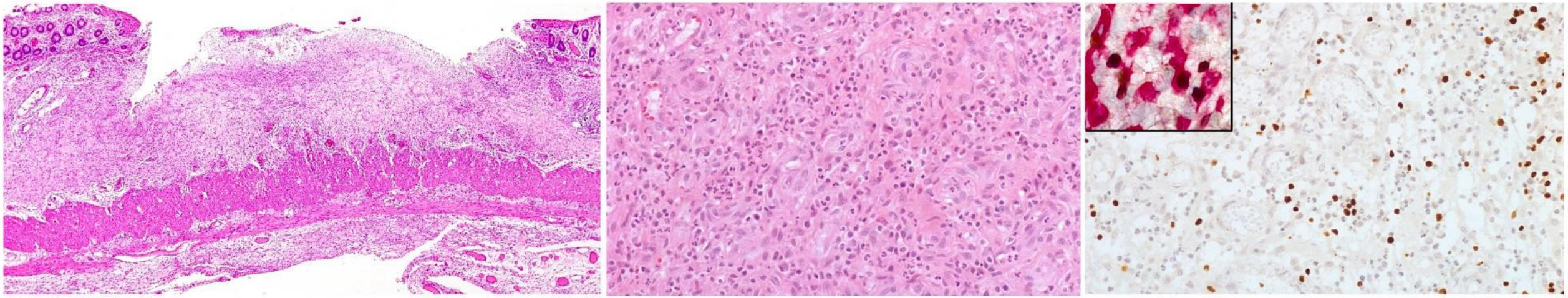
Liver at diagnosis | 1 year | 4 years




Patient wit chronic active EBV disease of T-cell phenotype with stable disease and liver morphology.

- The liver looks like viral hepatitis.

# Chronic active EBV disease of NK-cell type



CD56/EBER

- Gastrointestinal perforation
  - 4 year-old girl with history of severe mosquito bite allergy
  - NK-cell lymphocytosis in peripheral blood
  - High EBV DNA copy numbers in PB
  - History of intestinal perforation

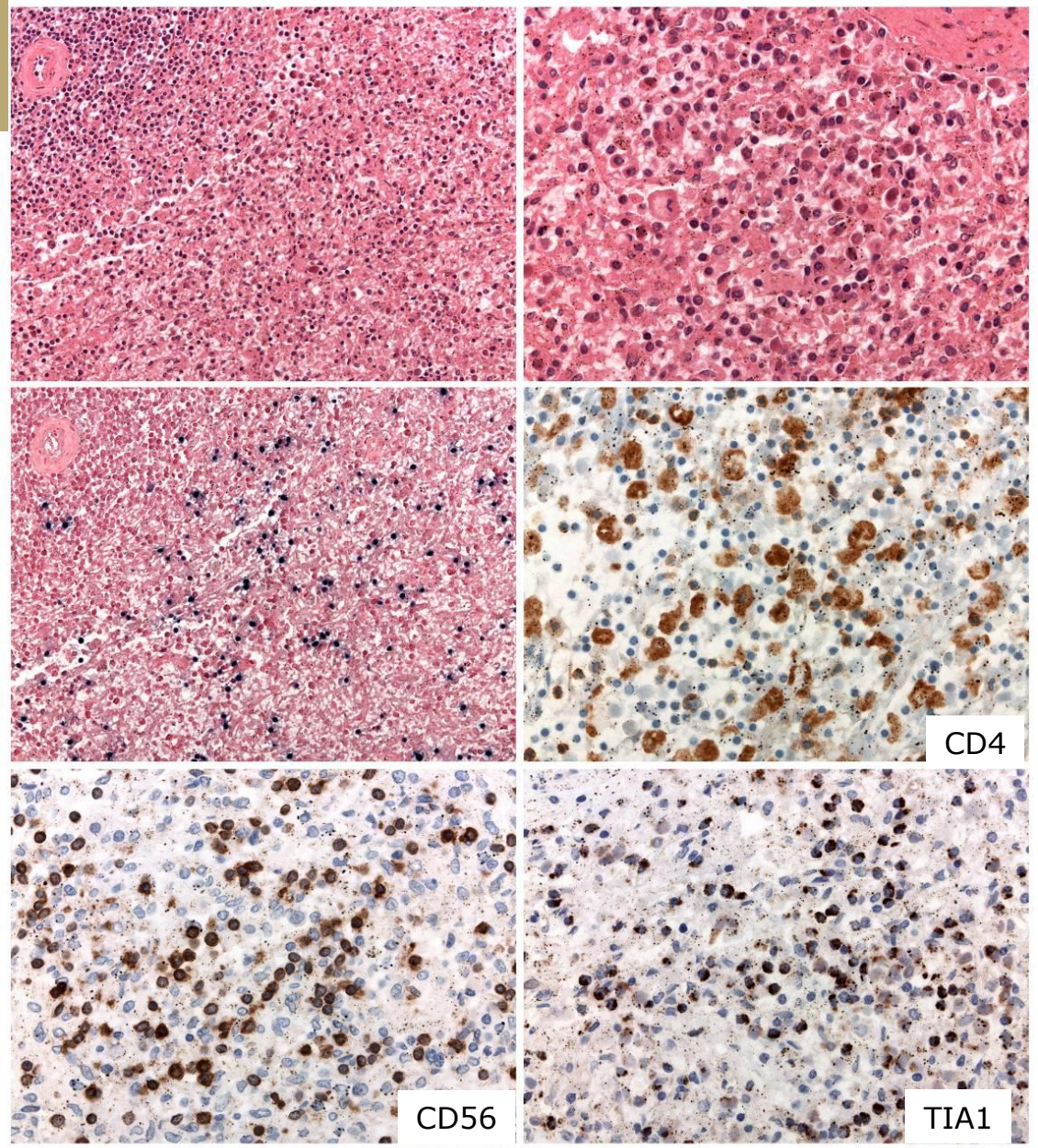
# CAEBV disease

- The spleen reveals athrophy of the white pulp
- Congestions of the red pulp
- Erythrophagocytosis

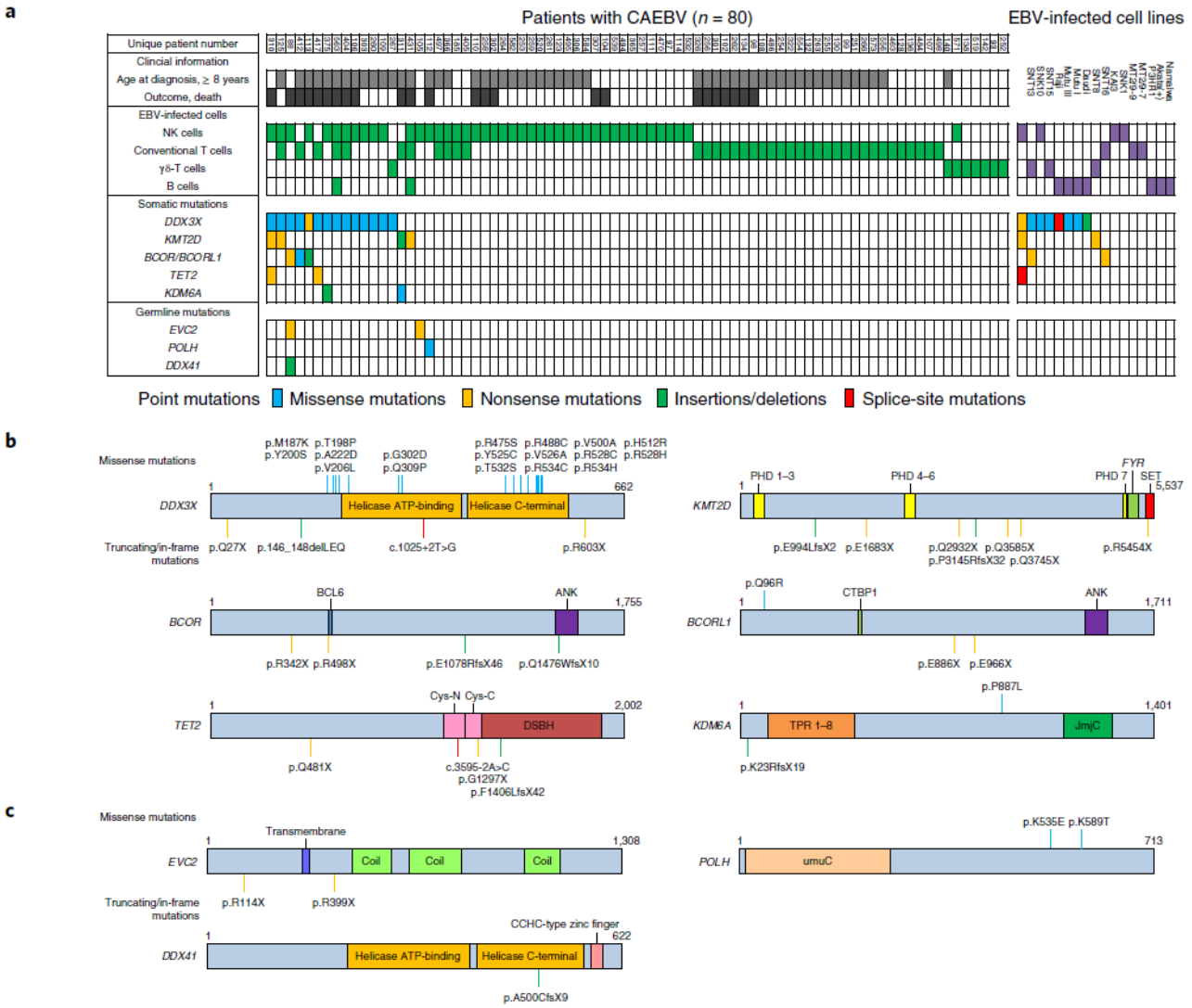
- HLH is rare in CAEBV disease but it presence might herald progression of the disease

T-cell phenotype in 60% of cases
CD4>CD8

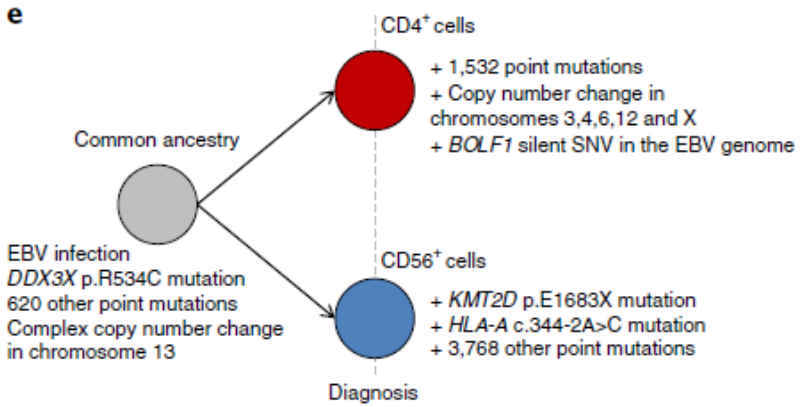
NK-cell phenotype in 40% of cases



# Chronic active EBV disease




- CAEBV especially the NK-type carry mutations already described in NK/T cell lymphoma, except *TP53*
- In CAEBV patients, EBV infects a common ancestor from which pre-malignant cells evolved by acquiring mutations (*DDX3X*) eventually leading to clonal evolution.




NATURE MICROBIOLOGY | VOL 4 | MARCH 2019 | 404–413 | www.nature.com/naturemicrobiolo

Comprehensive Cancer Center Tübingen – Stuttgart

Universitätsklinikum Tübingen

Eberhard Karls Universität Tübingen

# Systemic EBV-positive T-cell lymphoma of childhood

- **Definition:** Clonal proliferation of EBV-infected T-cells with an activated cytotoxic phenoptype (TIA-1+)

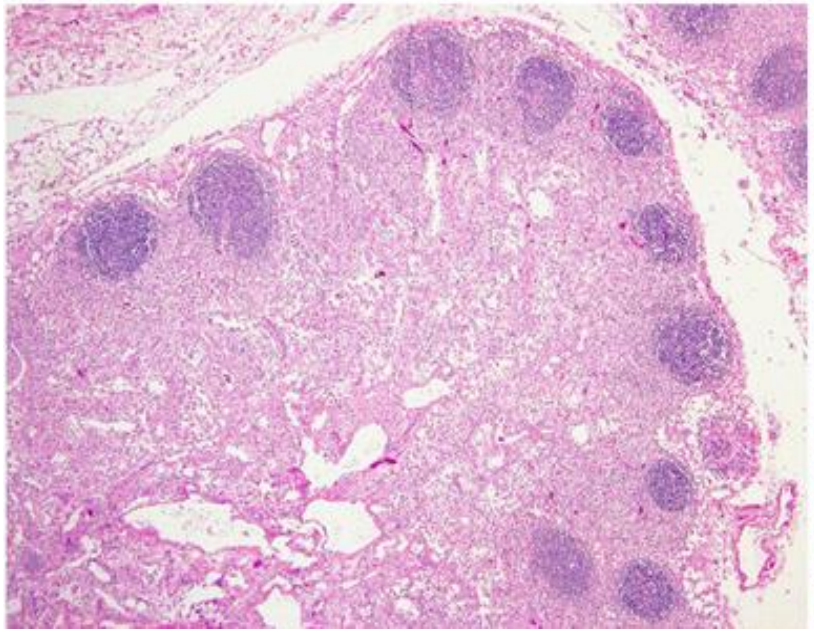
- Occurs shortly after primary acute EBV infection or rarely in the setting of chronic active EBV infection (CAEBV) mainly presents with hepatosplenomegaly and hemophagocytic syndrome (HLH)

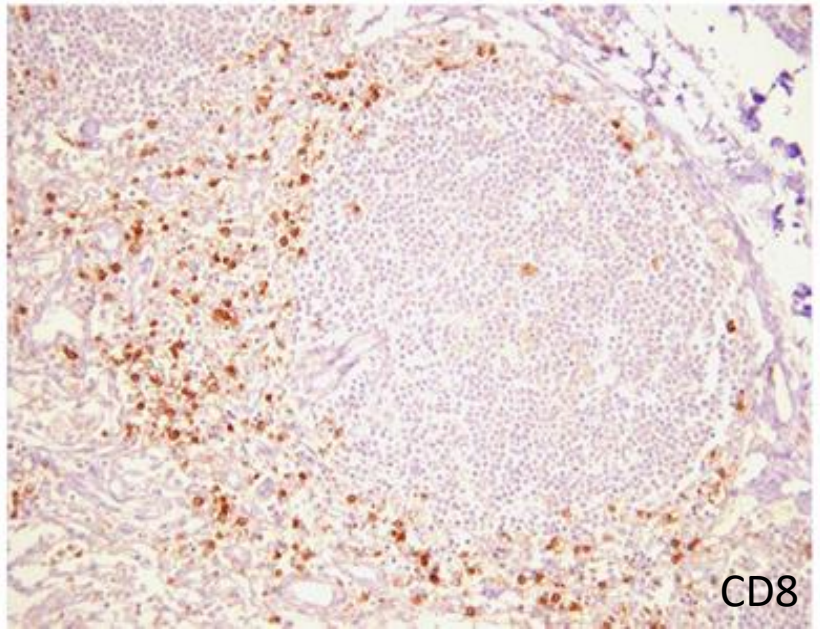
- **Prognosis:** Clinically has a rapid progression with multiple organ failure, sepsis and death, usually from days to weeks
  - No known immunodeficiency
  - Abnormal serologic response to EBV
  - It has a strong racial predisposition in Asians, Mexicans and rarely in whites

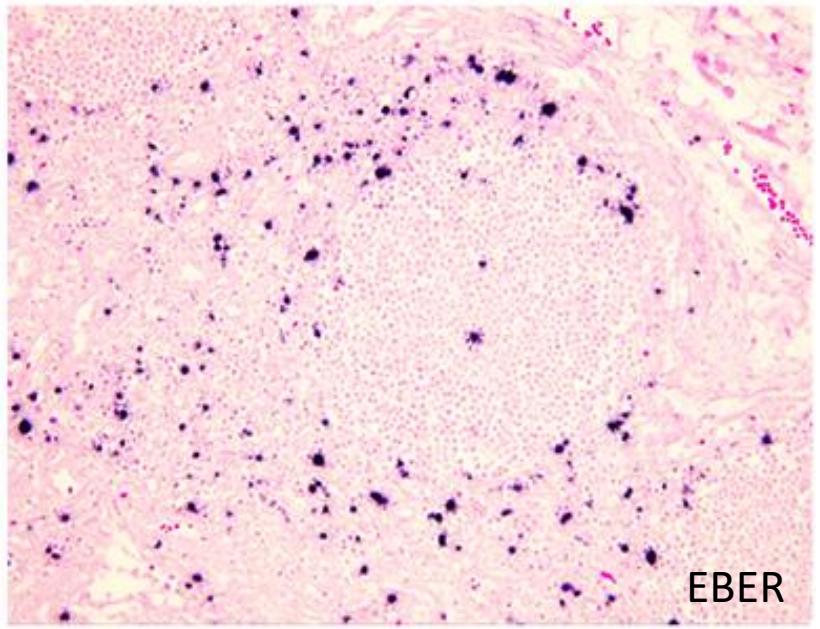
- **Diagnosis:** TCR clonal analysis and EBER ISH are required for the diagnosis

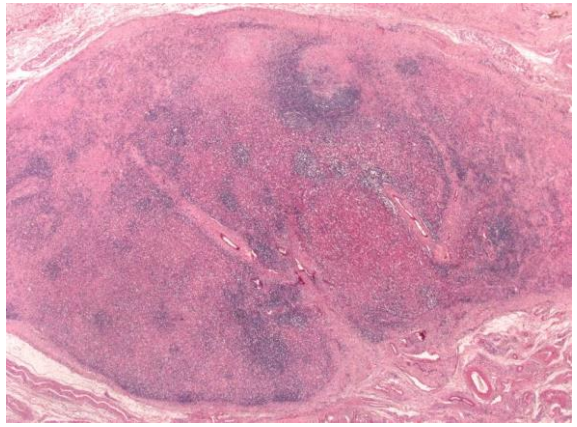
*Quintanilla-Martinez et al., Blood 2000;96:443-451*

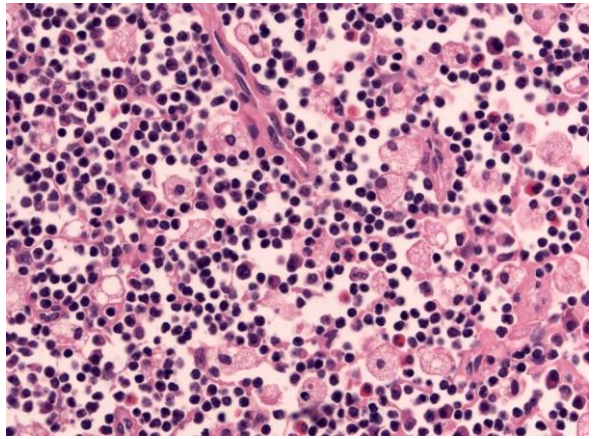
# Systemic EBV-positive T-cell lymphoma of childhood



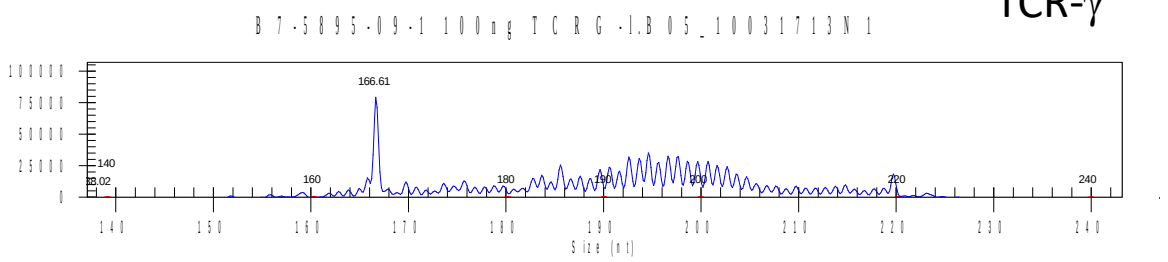




TCR-γ



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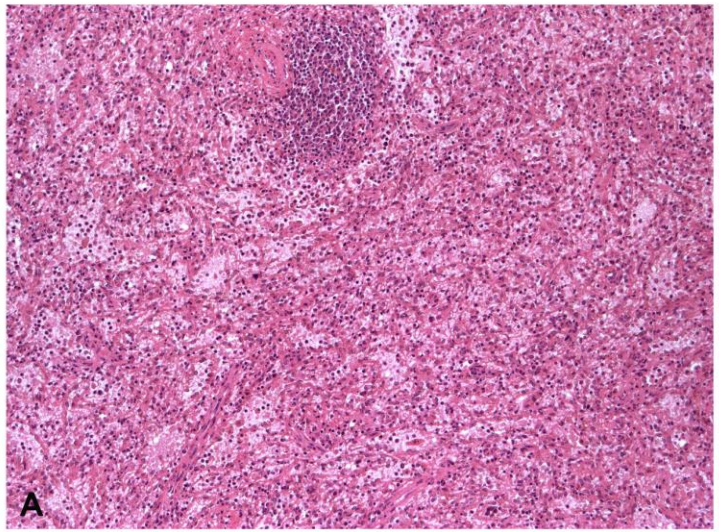
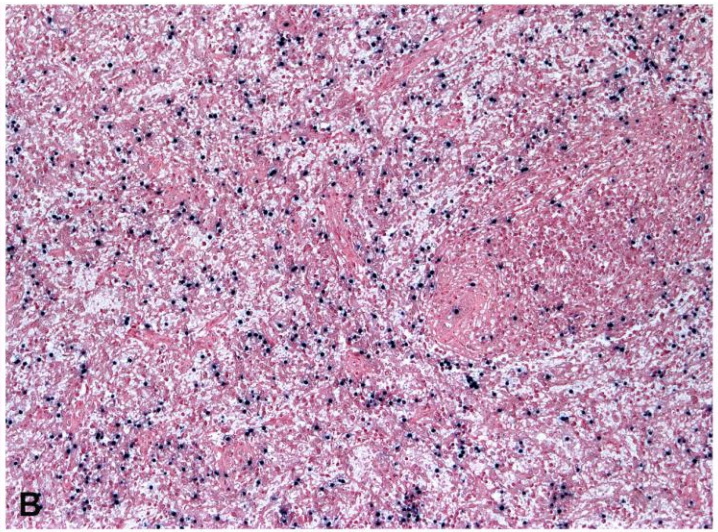
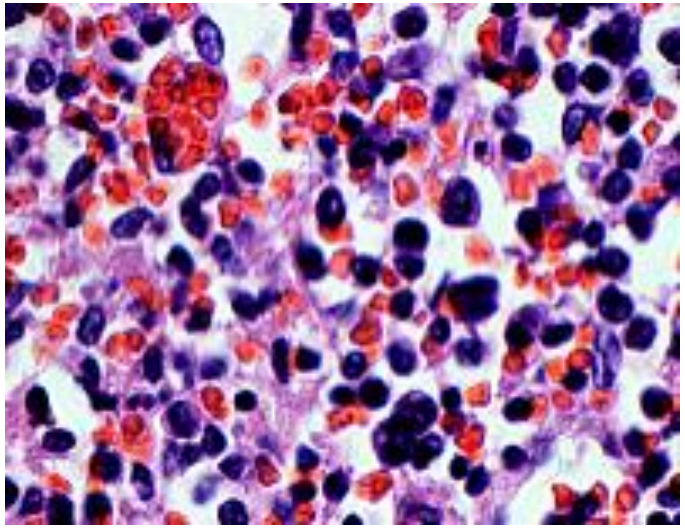
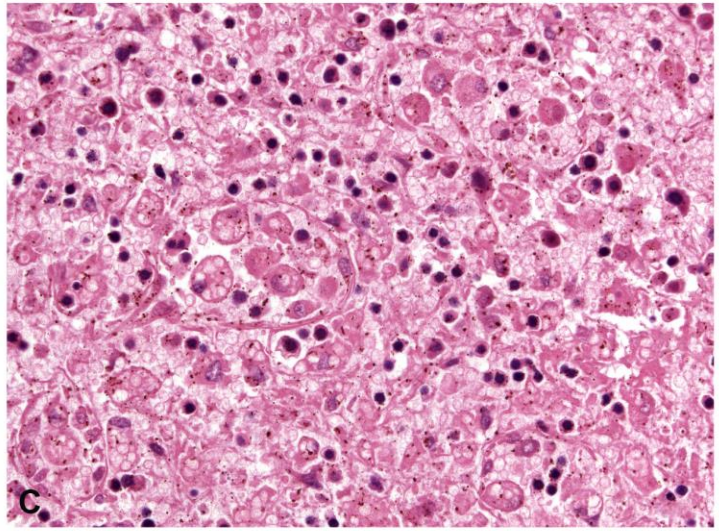
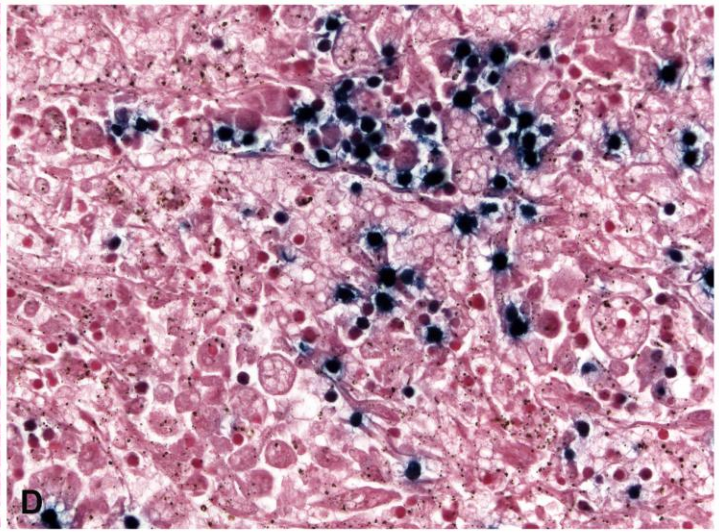


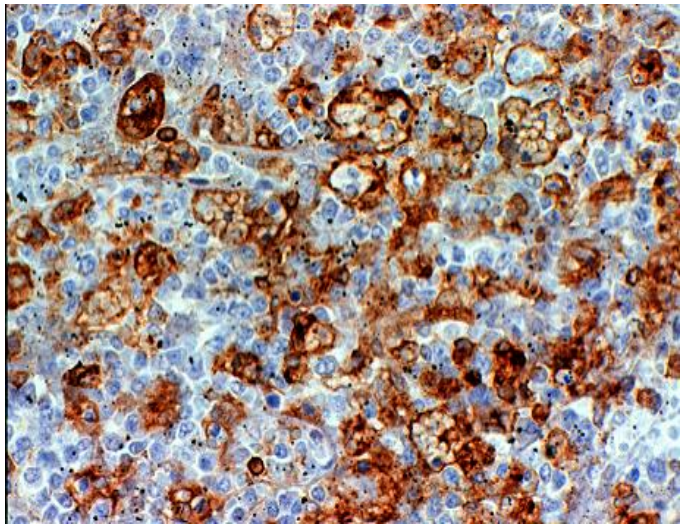



Striking hemophagocytosis

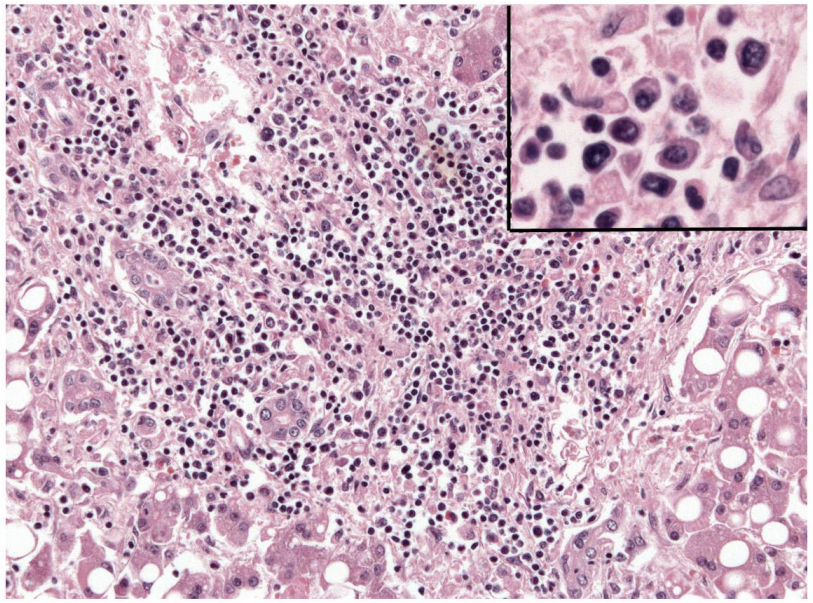


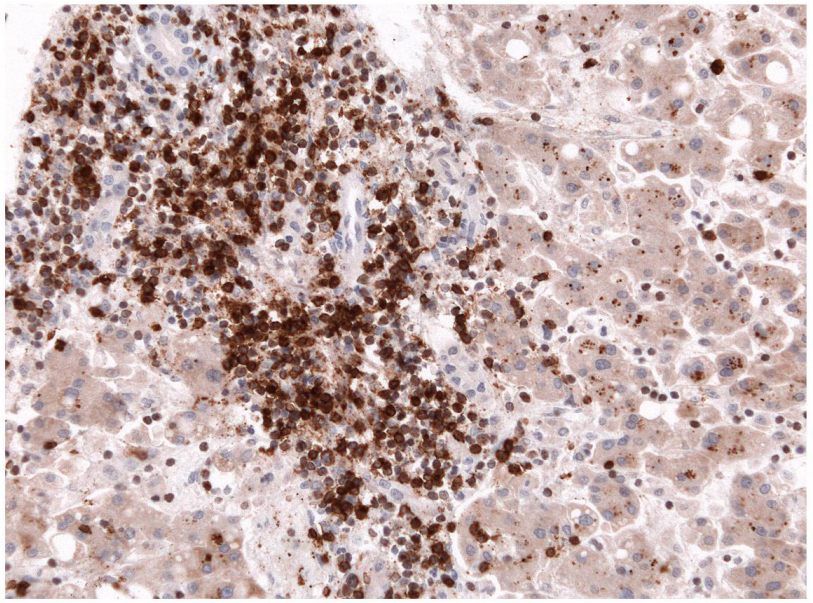



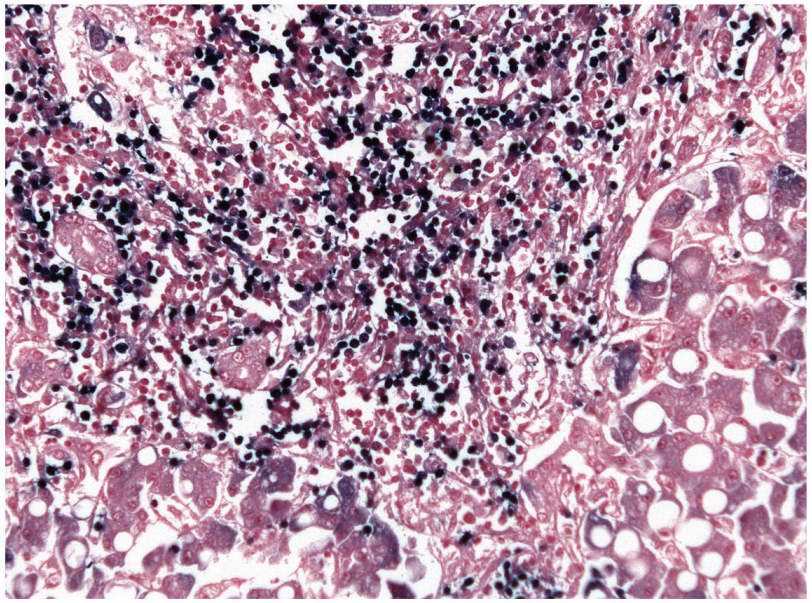



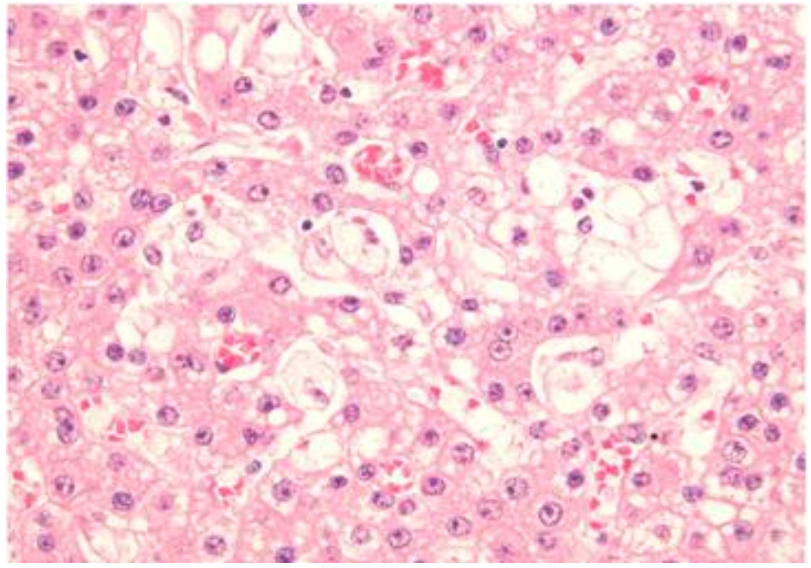
CD4+

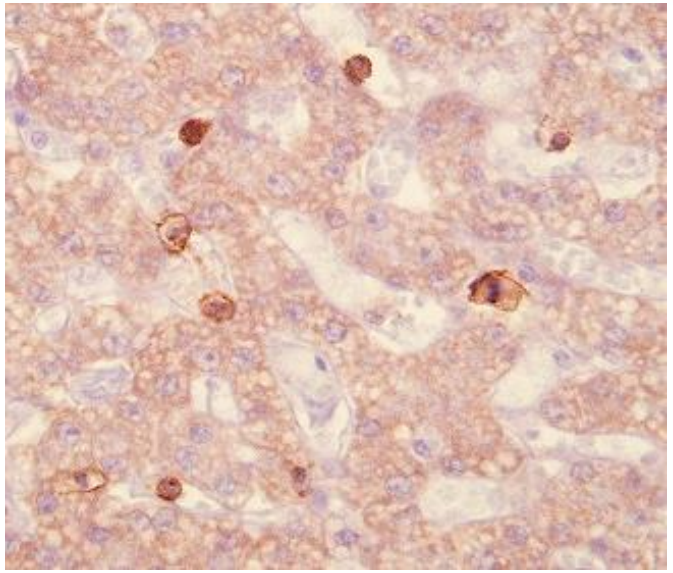
# Systemic EBV-positive T-cell lymphoma of childhood

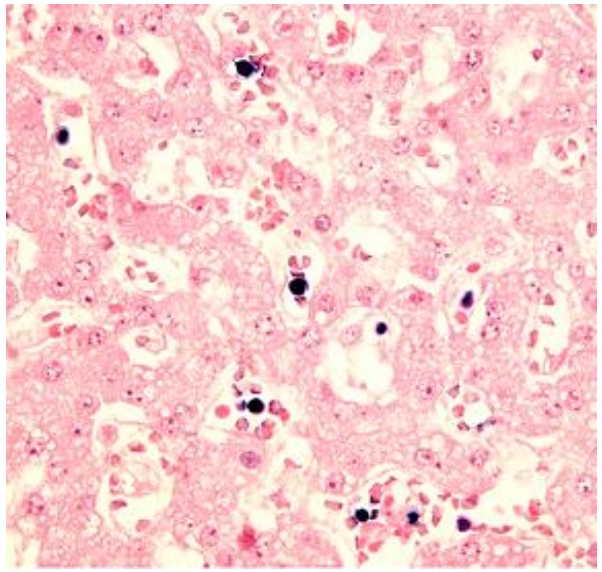






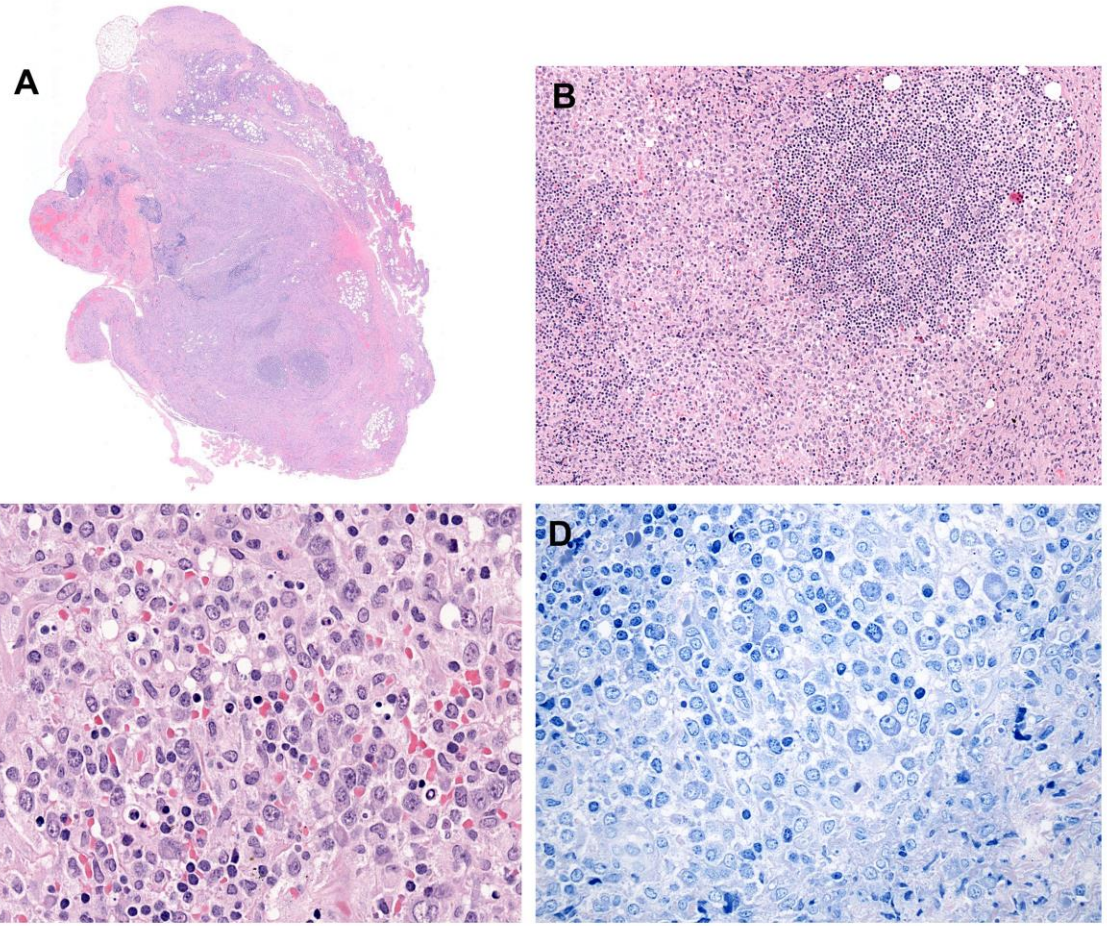


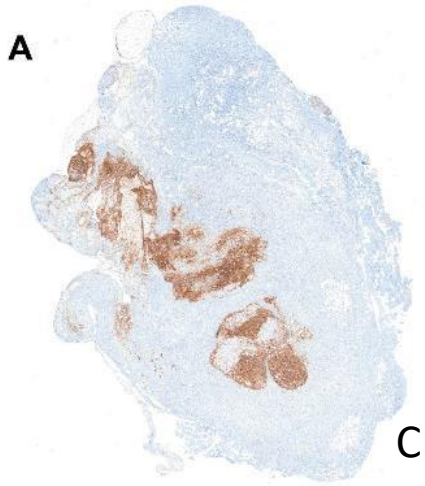




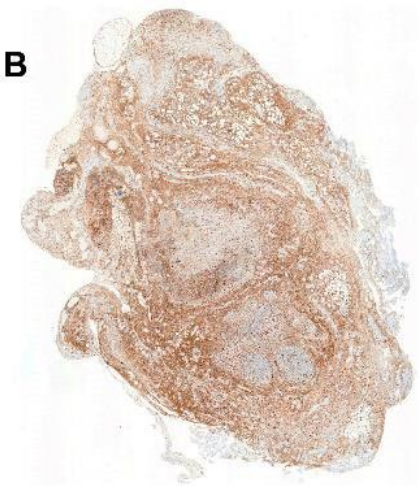
# Systemic EBV-positive T-cell lymphoma of childhood

Presenting predominantly as lymphadenopathy
Reported in Peru
Always CD8+

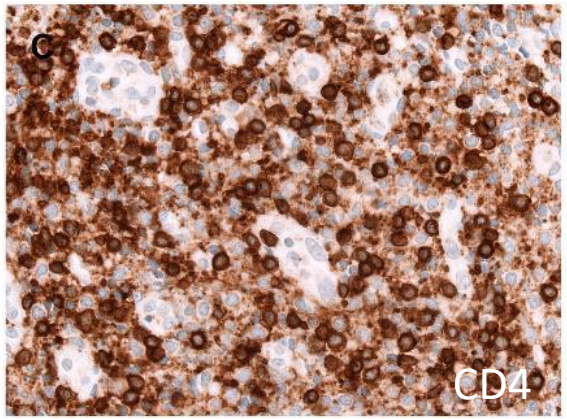


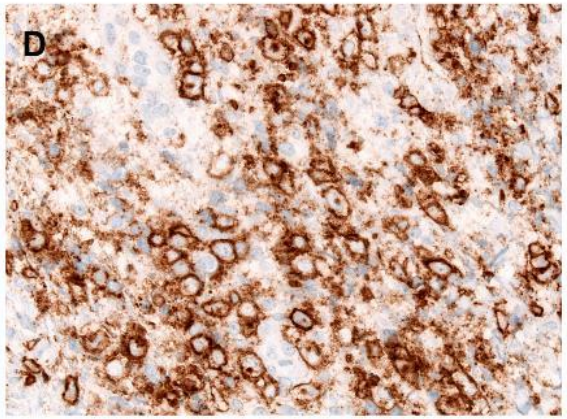




CD20

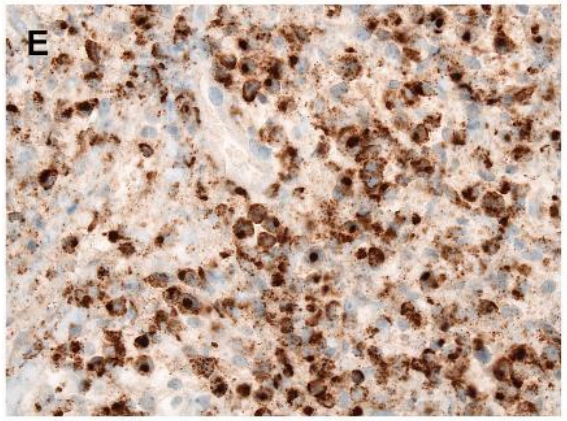



CD3

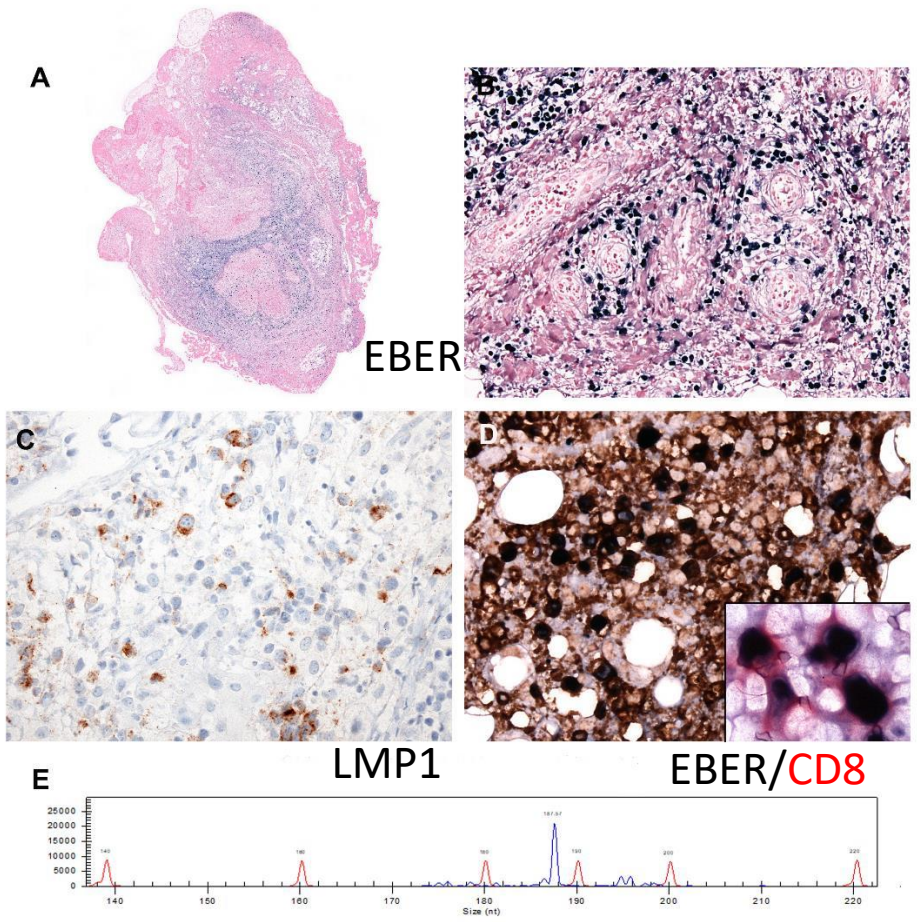



CD8



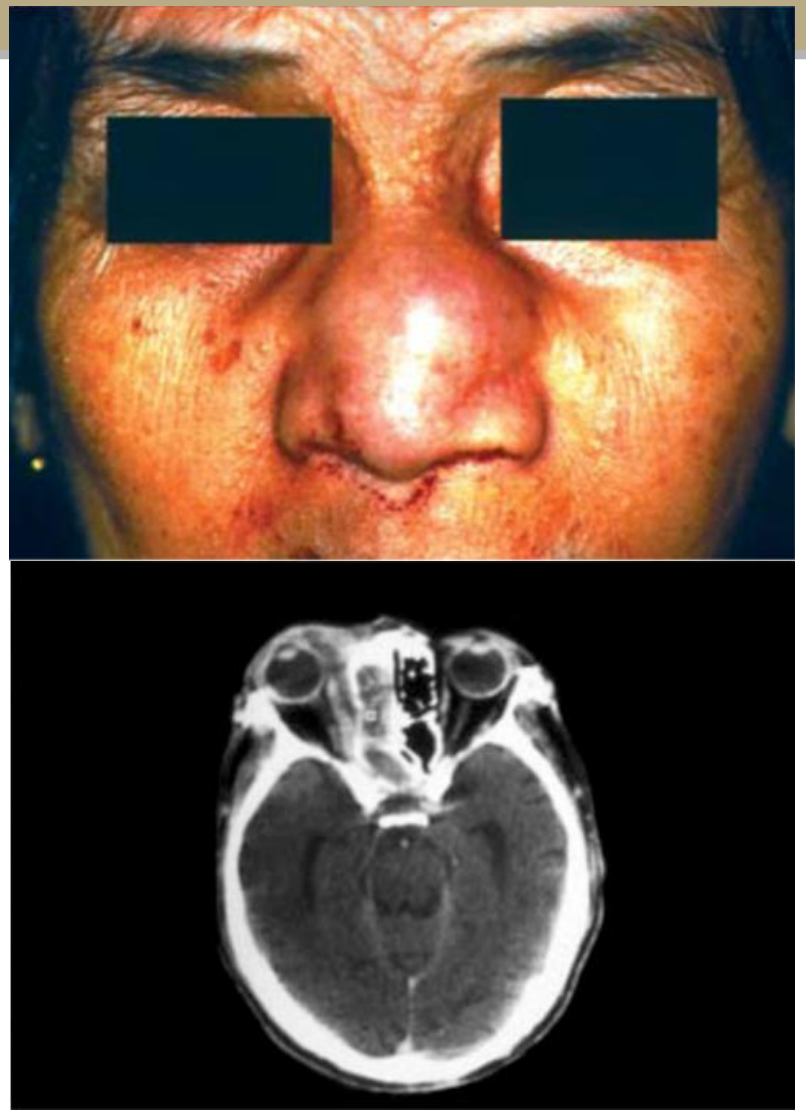

TIA1




| Disease | Clinical features | Morphology | phenotype | clonality |
|---|---|---|---|---|
| Non-familial EBV-associated HLH (complicated IM) | Diagnostic criteria for HLH should be fullfilled (≥ 5 criteria)<br>• Fever >38.5 °C<br>• Splenomegaly<br>• Cytopenias<br>• Hypertriglyceridemia<br>• Hemophagocytosis<br>• Low/absent NK cell activity<br>• Elevated ferritin<br>• Elevated CD25 | Hemophagocytosis in BM, spleen or LN´s<br><br>Relatively small numbers of EBV+ T cells<br><br>Bland cytology | Cytotoxic CD8+ cells (80%)<br><br>CD56+ cells raises the diff dx with ANKL and CAEBV | Monoclonal TCR in 50-60%<br><br>Cytogenetic analysis should be normal |
| CAEBV disease | IM-like illness > 3months<br><br>Protracted clinical course<br><br>Risk of progression to EBV+ T or NK lymphoma<br><br>HLH only during disease progression | Non-specific inflammatory changes with no evidence of lymphoma<br><br>LNs follicular hyperplasia, expanded paracortical areas<br><br>Bland cytology | T cell 60% CD4>>CD8>γδ<br><br>NK cell 40% | Monoclonal TCR in 40-63%<br><br>Monoclonal EBV 84%<br><br>Somatic mutations in DDx3D and KMT2D |
| Systemic EBV+ T-cell lymphoma of childhood | Occurs shortly after IM.<br>Abnormal serology against EBV with lack of anti-VCA IGM<br>Fulminant clinical course<br>HLH always | Cytological atypia ranges from minimal to severe<br><br>LN look depleted. Often BM, spleen and liver involvement | Predominantly cytotoxic CD8+ T cells<br><br>Rare CD4 or double CD4/C8+ | Monoclonal TCR in 100%<br><br>Cytogenetic abnormalities and somatic genetic alterations favor this diagnosis over HLH |

*Dojcinov S and Quintanilla-Martinez L, AJCP 2022*

# Extranodal NK/T cell lymphoma, nasal type

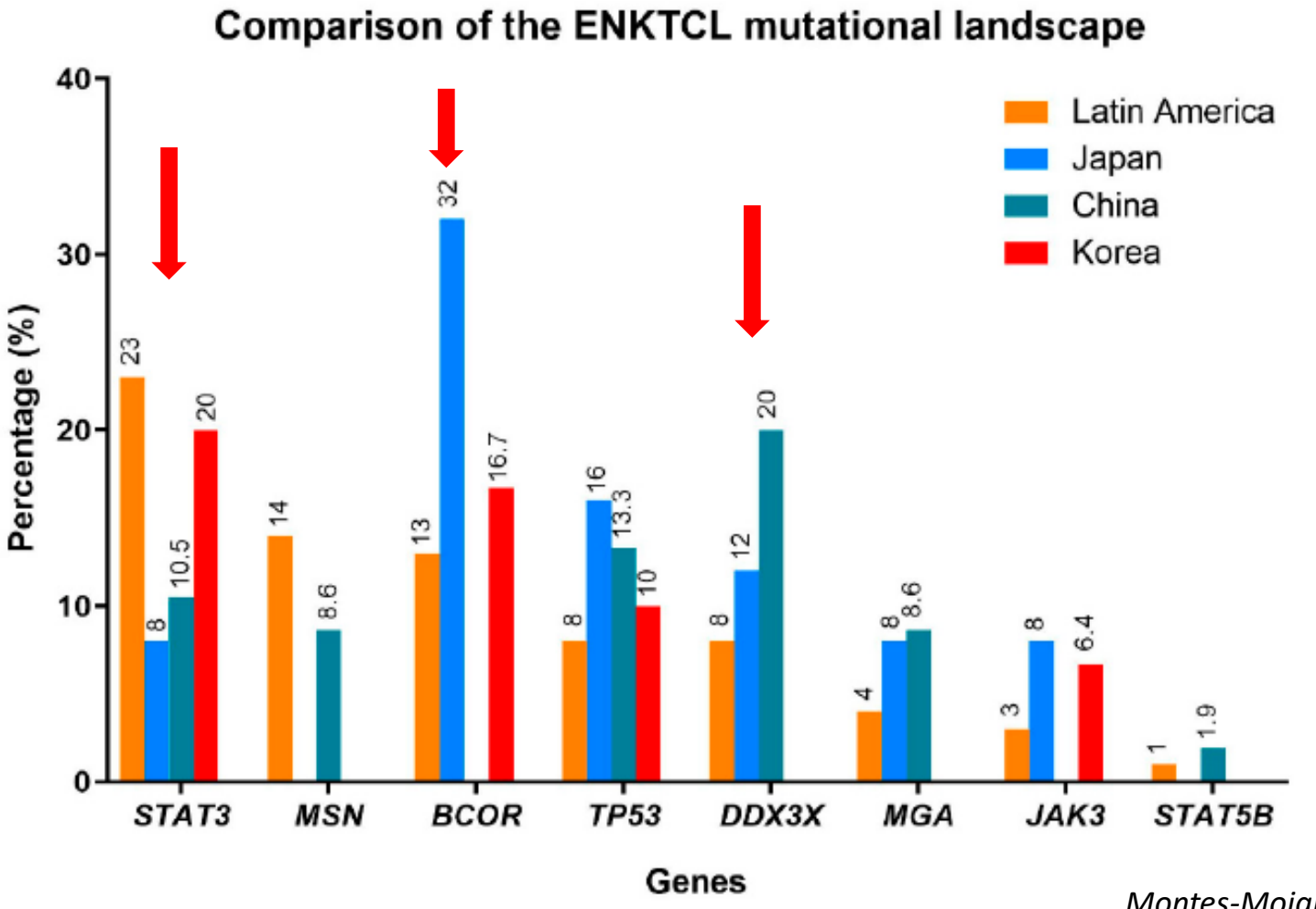


- **Epidemiology:** Prevalent in Asians and in the native American population of Mexico, Central America and South America
- SNP (rs9277378) in the HLA-DBP1 allele which confers a 2.3 times risk of NKTL, play a crucial role in CD4 T lymphocytes for antigen presentation

- **Clinical features:** Patients with nasal involvement present with symptoms of nasal obstruction and epistaxis due to a midfacial destructive lesion (lethal midline granuloma). The lesion can involved nasopharynx, paranasal sinuses, orbit, oral cavity, palate and oropharynx.

*Chan JKC, Quintanilla-Martinez L, et al., WHO 2017*

# Extranodal NK/T cell lymphoma, nasal type



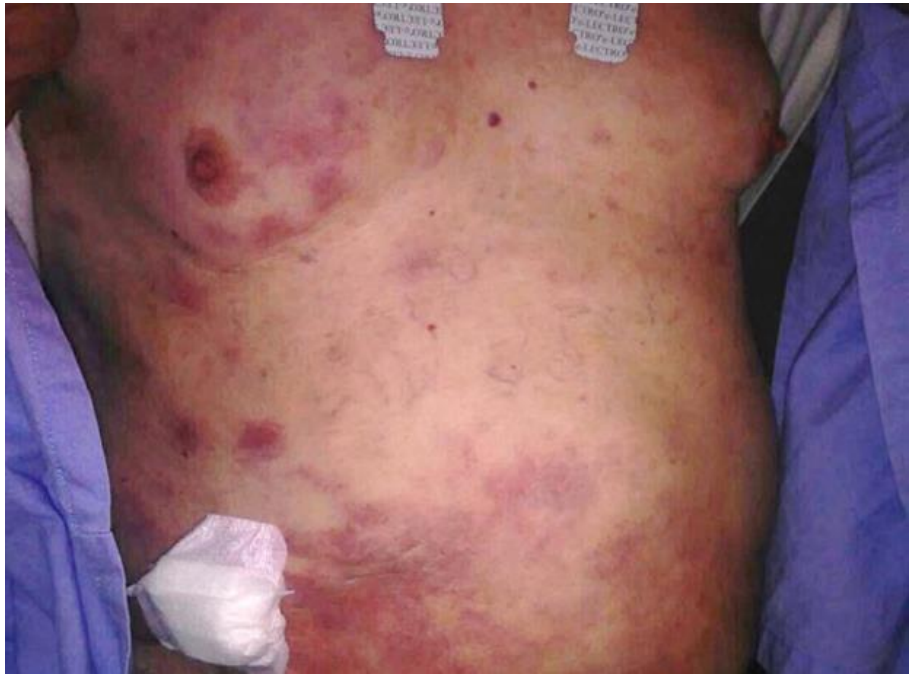

| Gene | Function | Frequency |
|---|---|---|
| STAT3 | Transcription activator, cell growth and apoptosis | 13 % |
| STAT5B | Transcription activator, cell growth and apoptosis | 1.7% |
| JAK3 | Role in innate and adaptive immunity and in hematopoiesis, cell growth, development and differentiation | 5.3% |
| DDX3X | RNA helicase activity, transcriptional regulation, translation, cellular signaling | 15.7 % |
| TP53 | Tumor suppressor, transcriptional activation, cell cycle arrest, apoptosis, DNA repair | 14.5 % |
| MGA | Transcriptional regulation | 6.4 % |
| MSN | Cell-cell recognition, cell movement | 6.1 % |
| BCOR | Germinal center formation, apoptosis, transcriptional corepressor | 16.6 % |

Dobashi et al., Genes, Chromosomes & Cancer, 2016

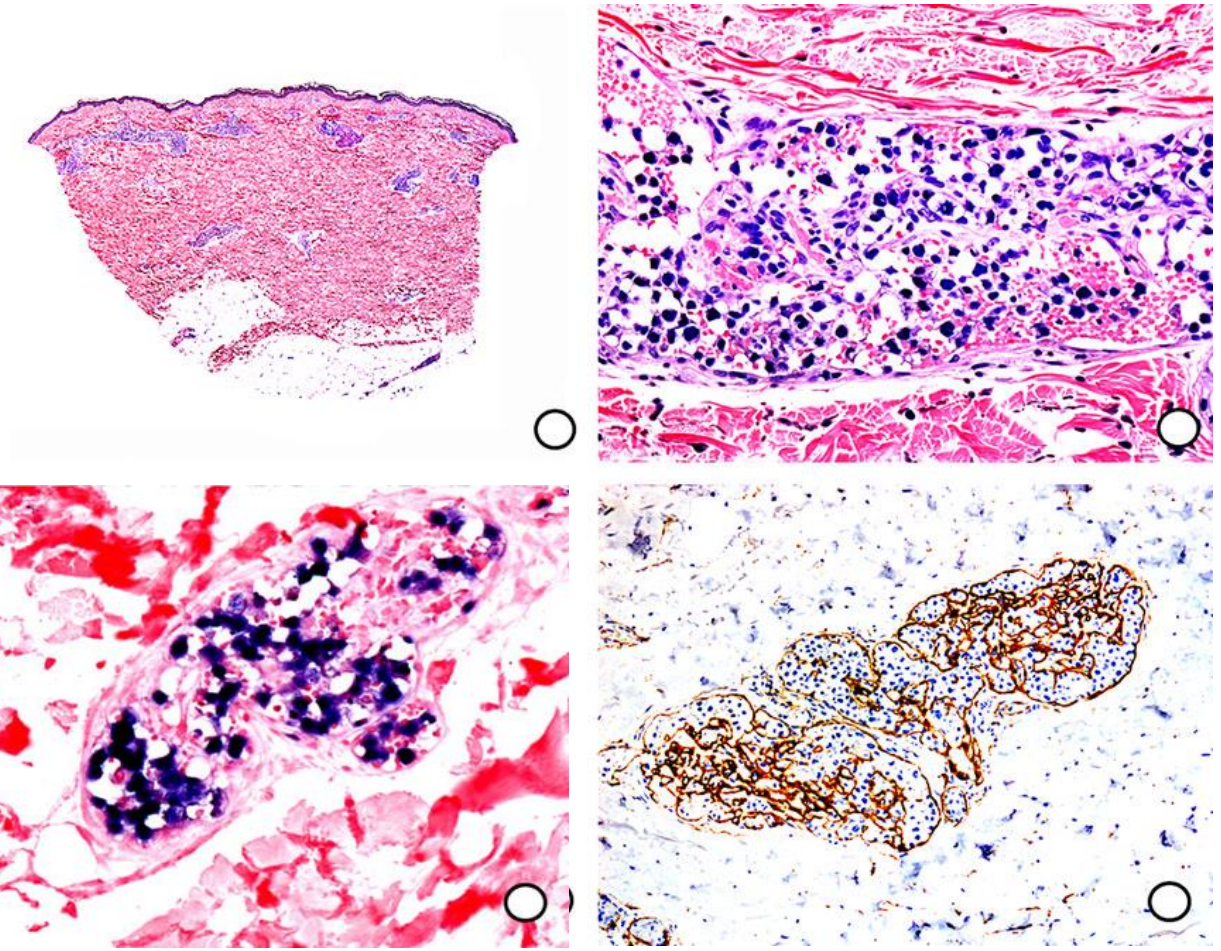
*Montes-Mojarro & Quintanilla-Martinez* Cancers **2021**, *13*, 1414

# Intravascular NK-cell lymphoma

- Very rare disease, representing < 3% of all intravascular lymphomas
- EBV- associated
- Skin and CNS frequently involved
- Cytotoxic lymphoma usually CD56+

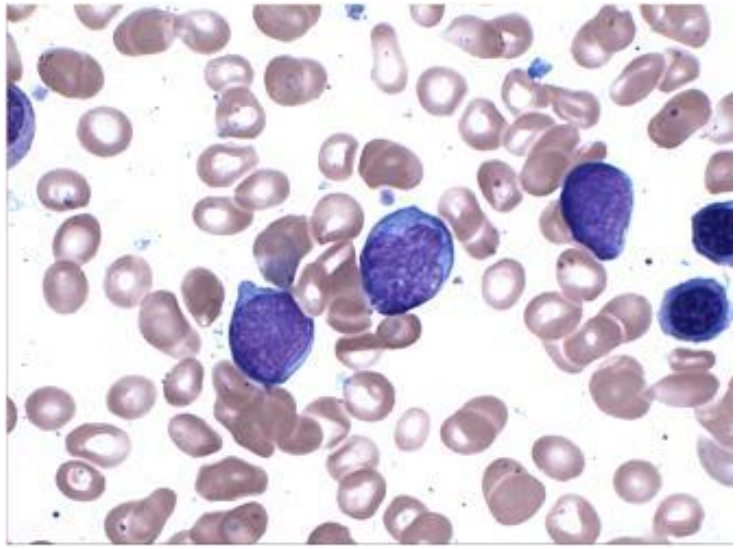




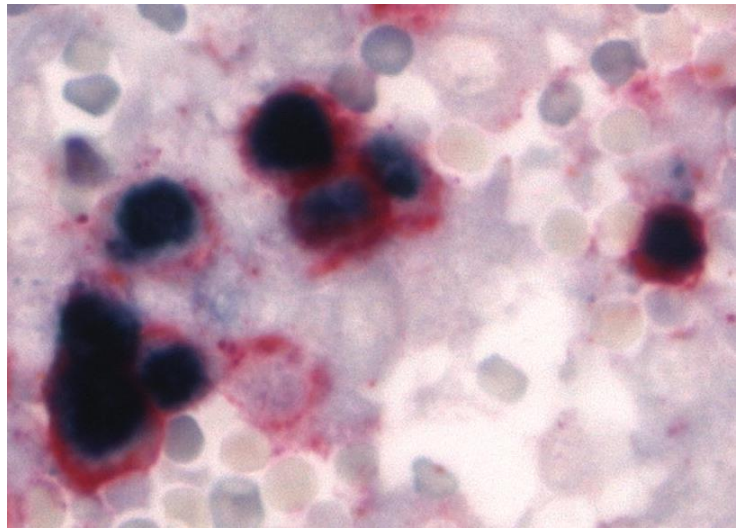


# Aggressive NK cell leukemia

- **Definition:** A neoplastic proliferation of NK-cells associated with Epstein-Barr virus and an aggressive clinical course.
- **Clinically:** Prevalent among Asians. Patients are young to middle age adults with a median of 39 years (range 23 -78). It involves usually the peripheral blood, bone marrow liver and spleen.



Peripheral Blood



Bone marrow

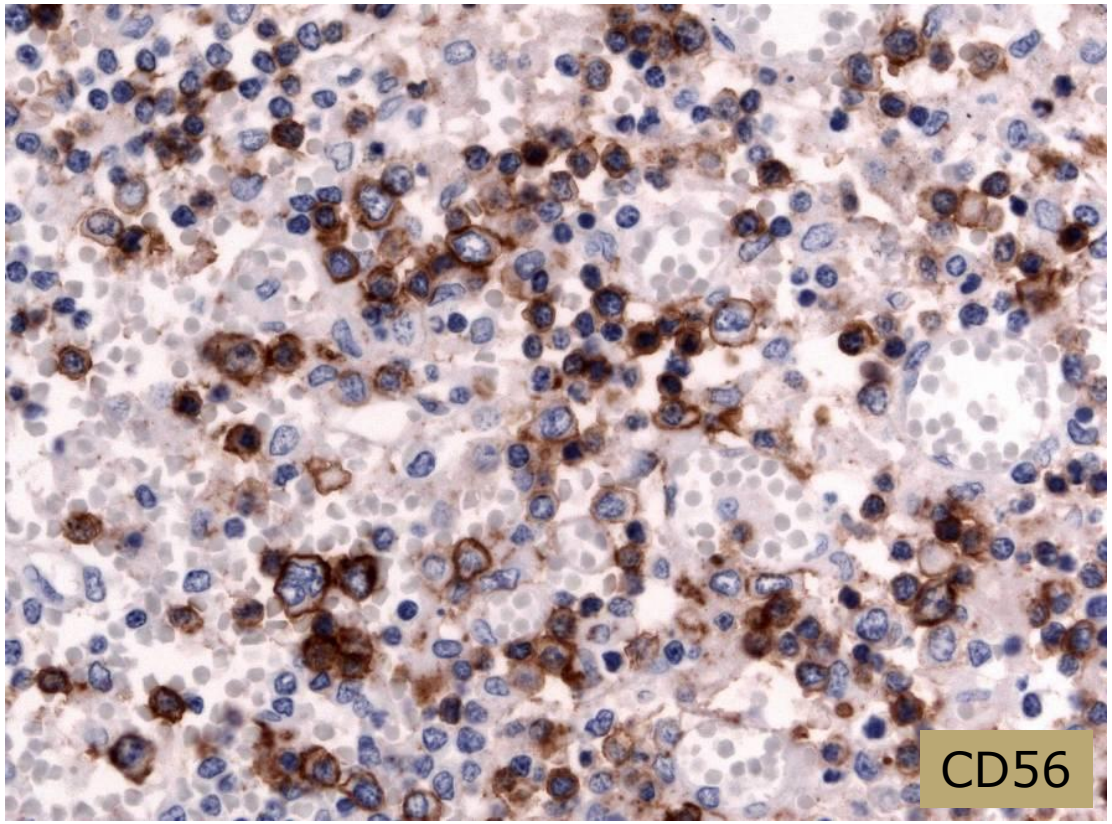
CD56/EBER

*Chan JKC, Jaffe ES, et al., WHO 2016*

# Aggressive NK cell leukemia

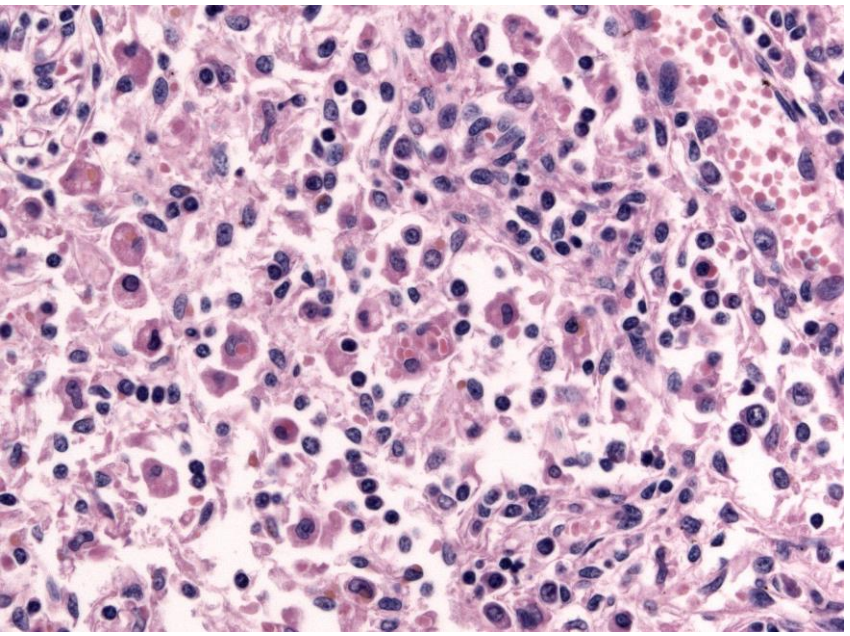
- **Morphology:**
  - Leukemic cells show a range of appearances from normal large granular lymphocytes to cells with very atypical nuclei with irregular foldings.
  - Infiltration might be massive, focal of sublte
  - Hemophagocytosis

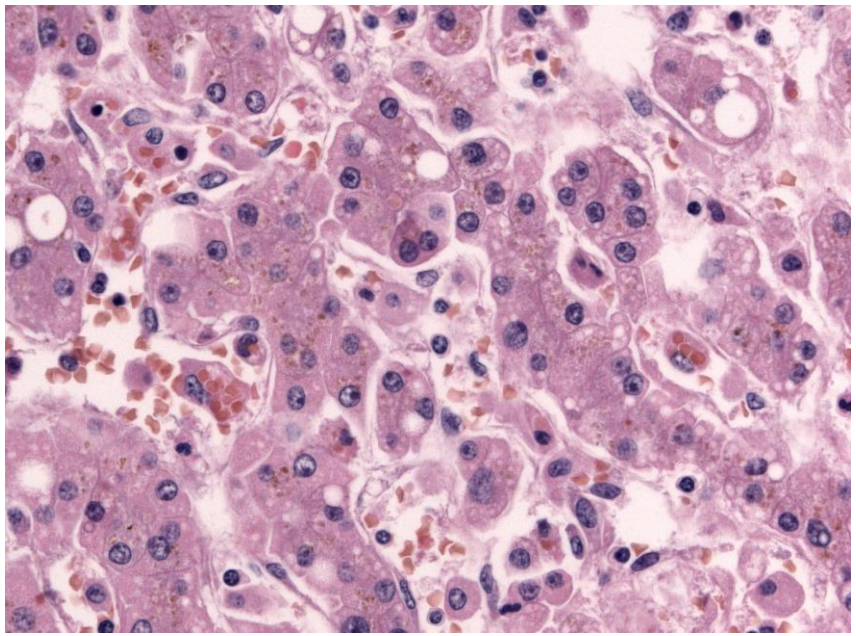
- **Prognosis:**
  - Clinically has a rapid progression with multiple organ failure, sepsis and death, usually from days to weeks after presentation

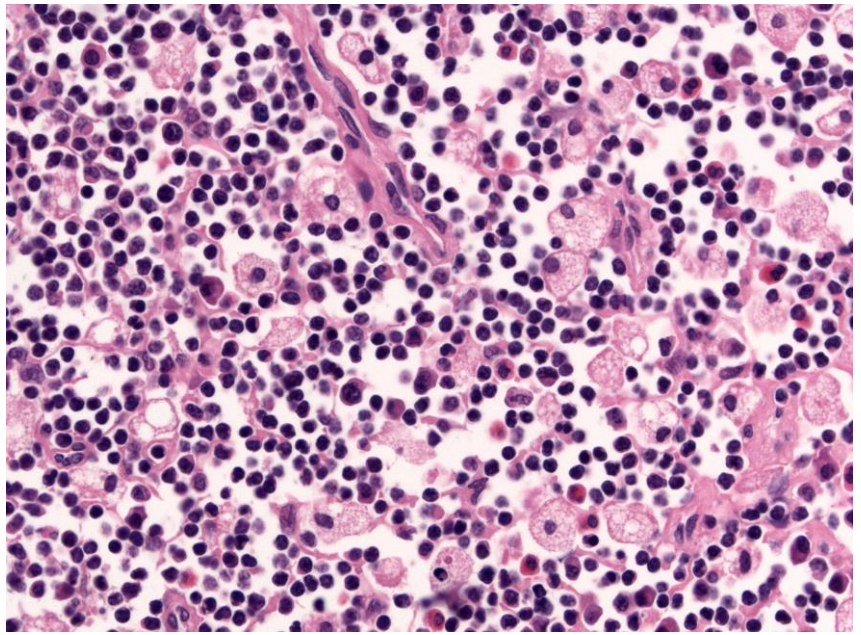


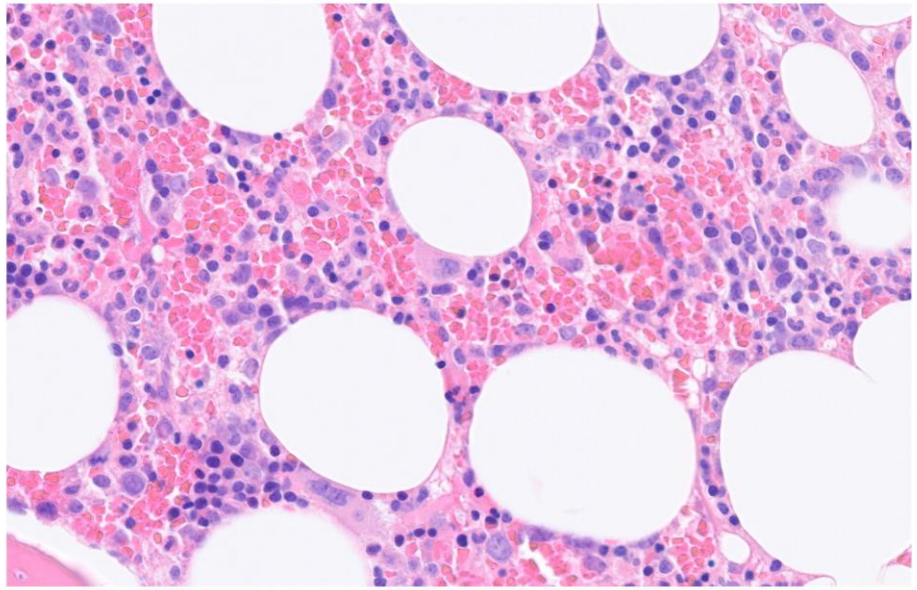

- It has overlapping features with systemic EBV+T-cell lymphoma of childhood (CD8+)

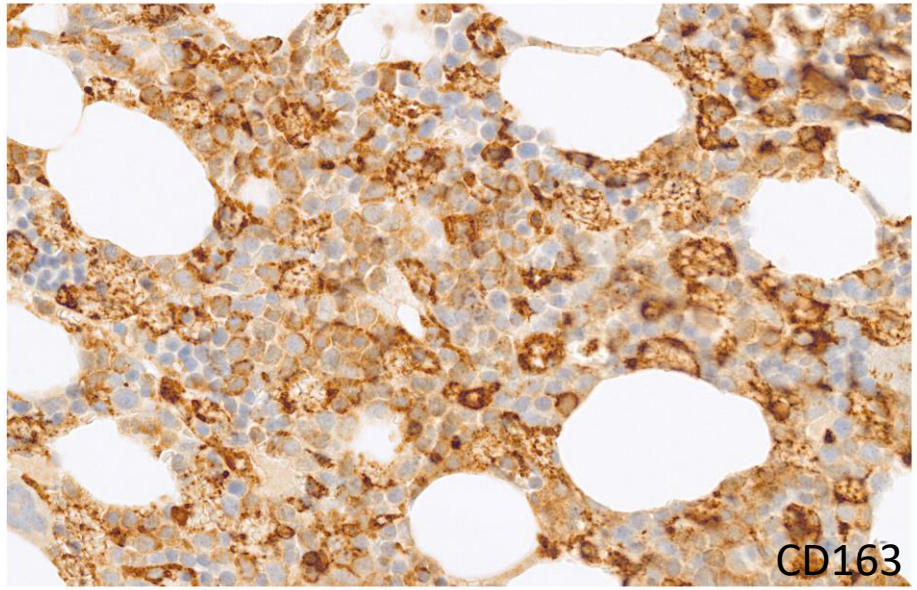
# Aggressive NK cell leukemia



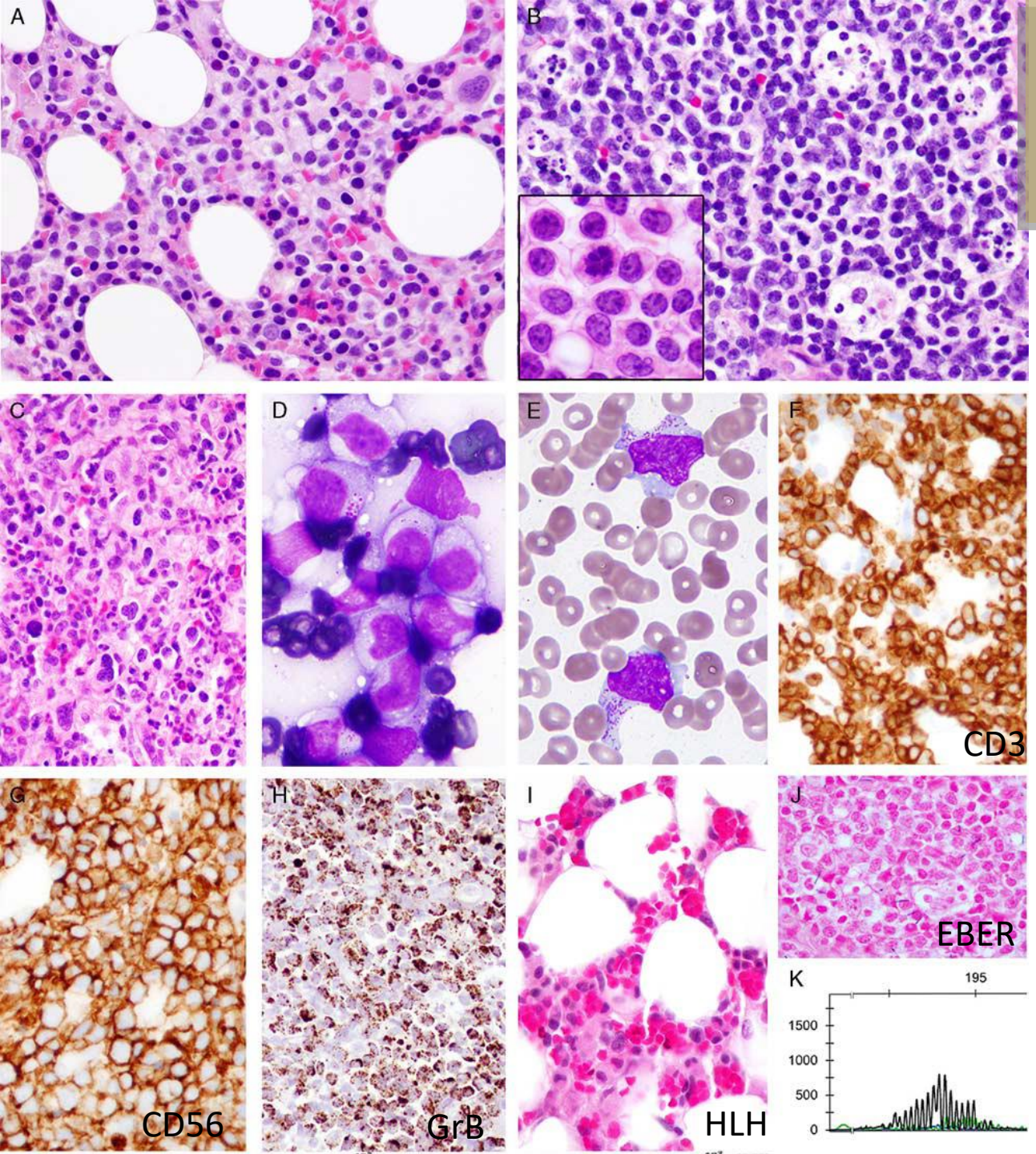








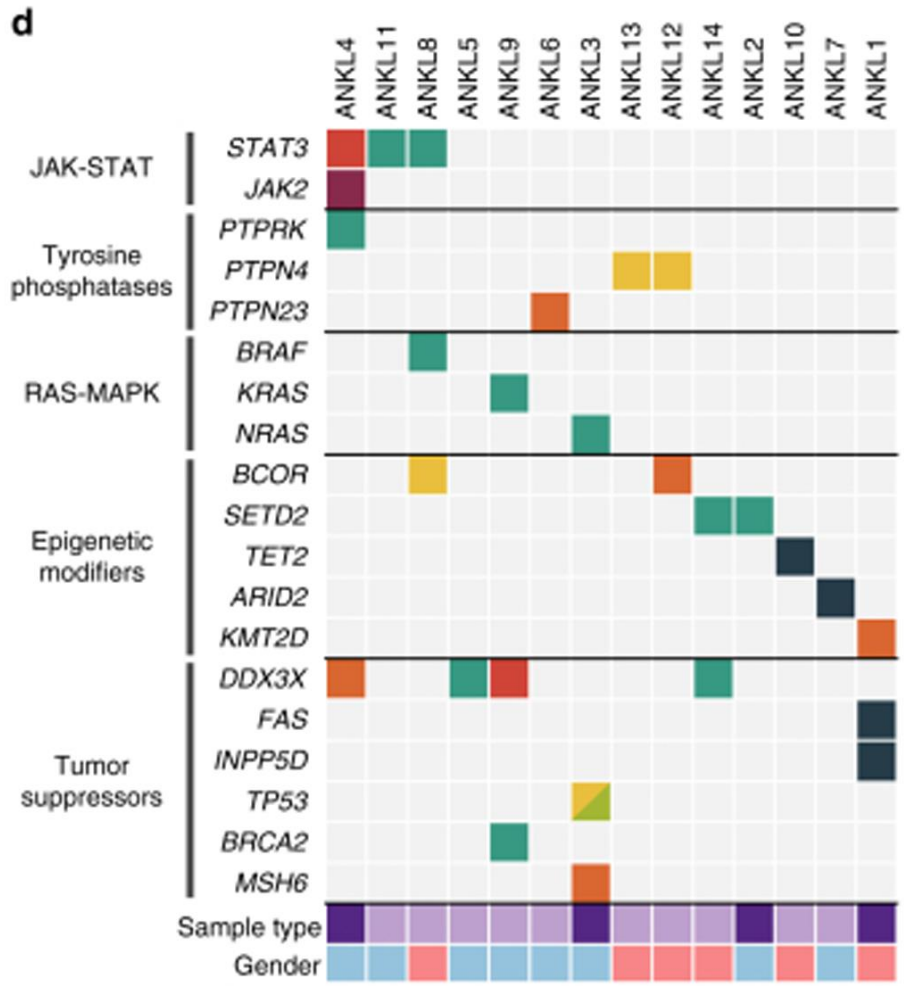
# Aggressive NK cell leukemia EBV-negative




- EBV- AKNL shares most clinical and pathological features with EBV+ AKNL
  - Median age 63 years (range 22 - 83 years
  - M:F ratio 2.5:1
- Mainly described in non-Asian patients
- Does not seem to share the racial predilection of the EBV+ cases
- Bone marrow involvement was present in 5/7 and hemophagocytosis in 3/7
- *STAT3* mutations in 2/2

Am J Surg Pathol Volume 41, Number 1, January 2017

# Aggressive NK cell leukemia



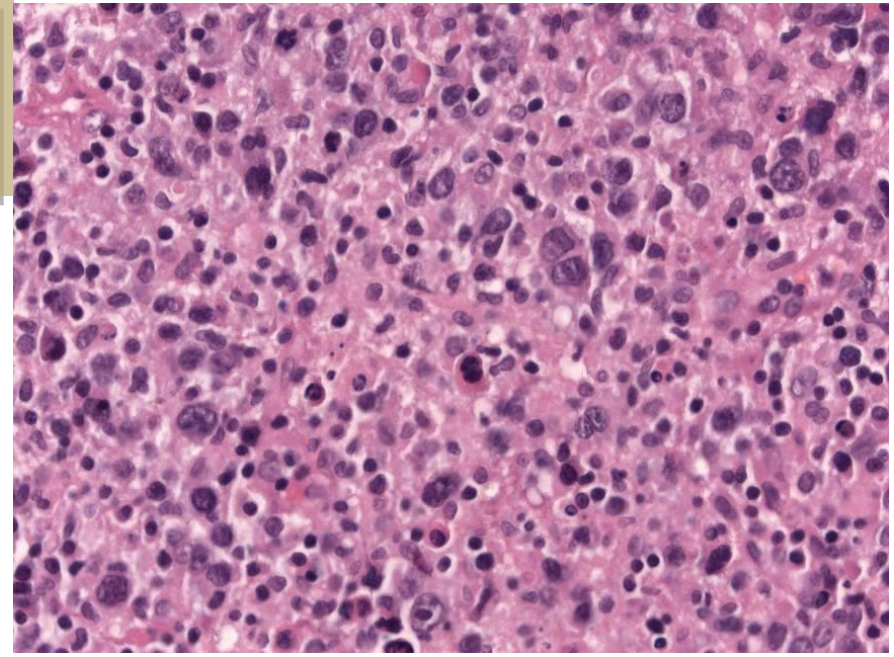

- Whole genome sequencing of 14 cases of ANKL
- *STAT3* (21%)
- RAS-MAPK pathway (21%)
- *DDX3X* (29%)
- Epigenetic modifiers (50%)

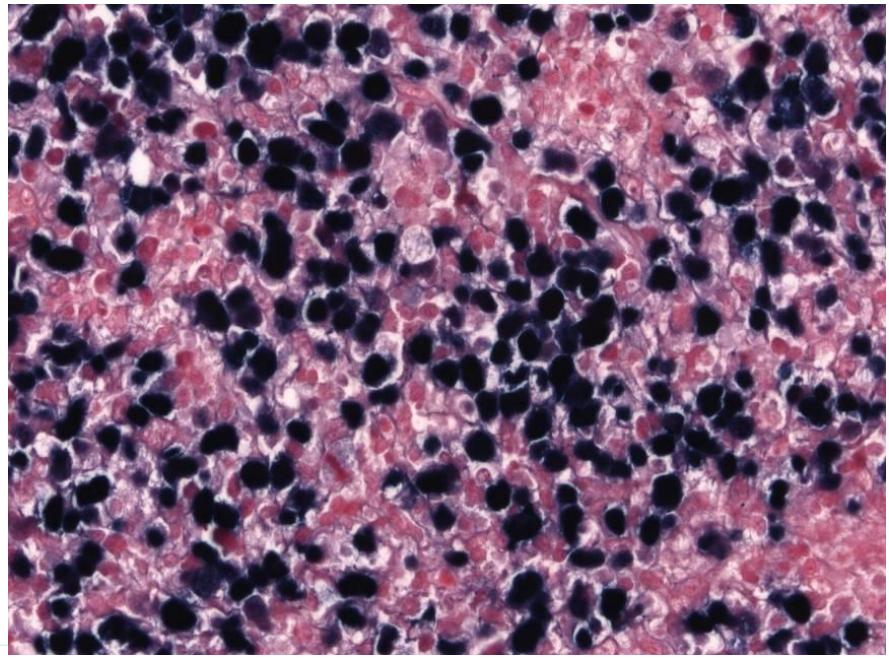
The genetic landscape from ANKL is very similar to the one described for ENKTCL

*Dufva et al, Nat Commun 2019 19:9:1567*

# Primary EBV+ nodal T- or NK-cell lymphoma

- Included as provisional entity in the ICC
  - Primary LN involvement, no nasal disease
  - Monomorphic or polymorphic, large cells
  - Cytotoxic phenotype (CD8+ and/or γδ+)
  - CD56 usually negative
  - variable expression of CD5
  - No geographic necrosis
  - Often associated with immunodeficiency
    - HIV, post-transplant, elderly





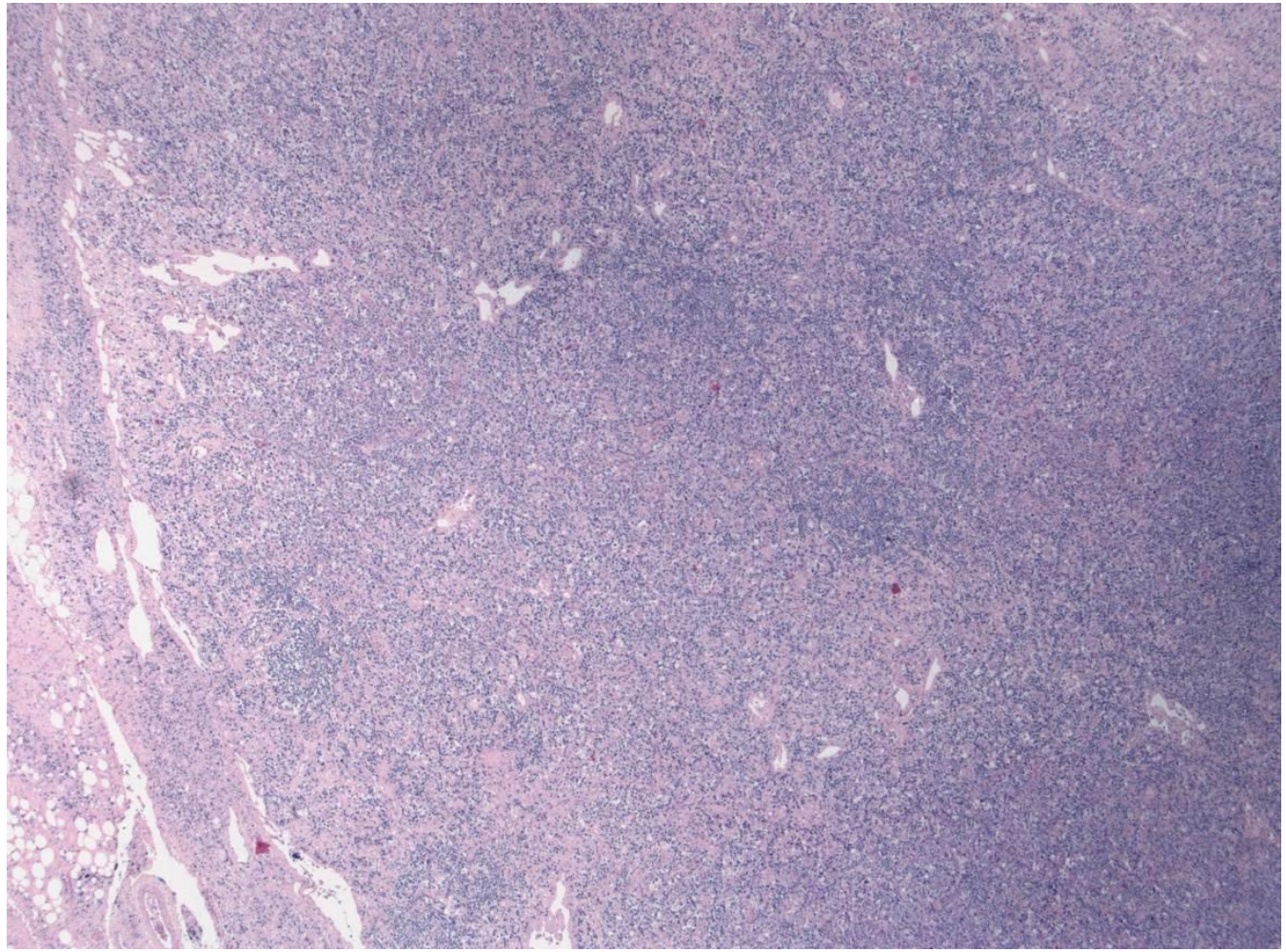
*Attygale A, et al Histopathology 2013*

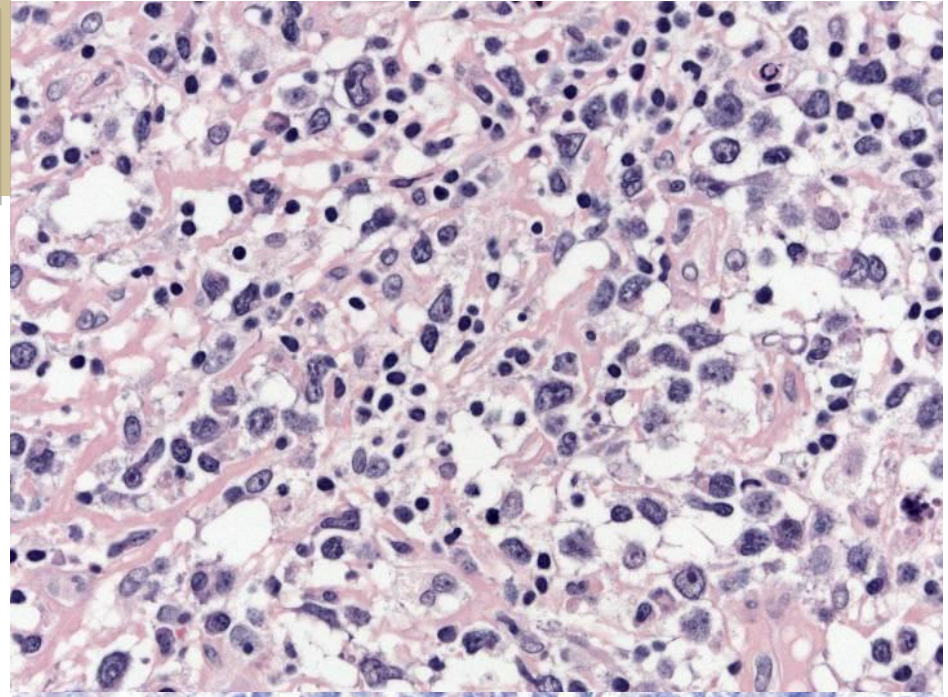
*Revised 2017 WHO classification*

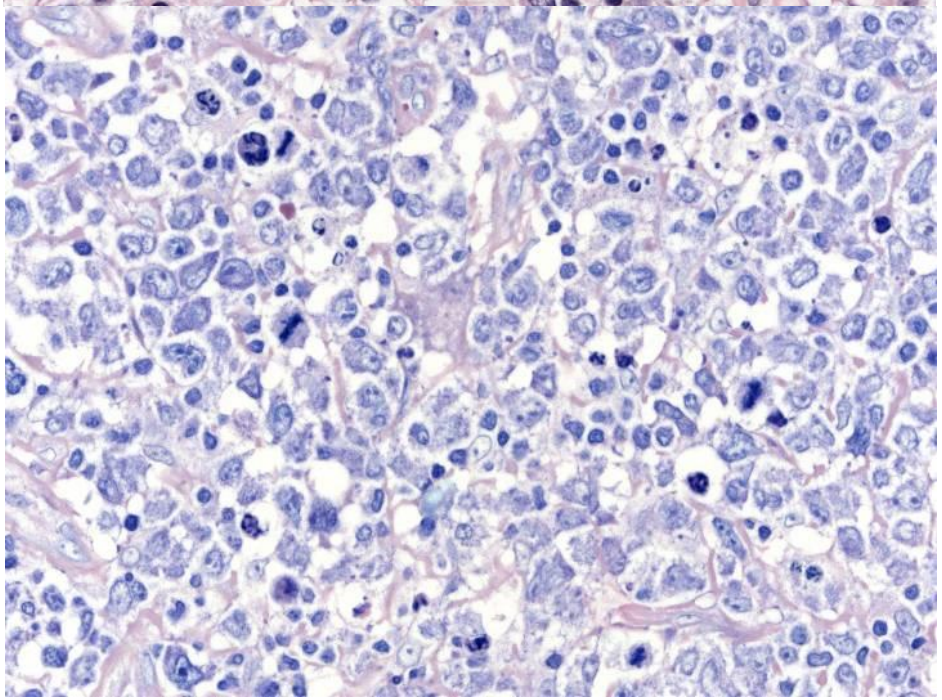
*Campo E, Blood 2022*

# Primary EBV+ nodal T or NK-cell lymphoma

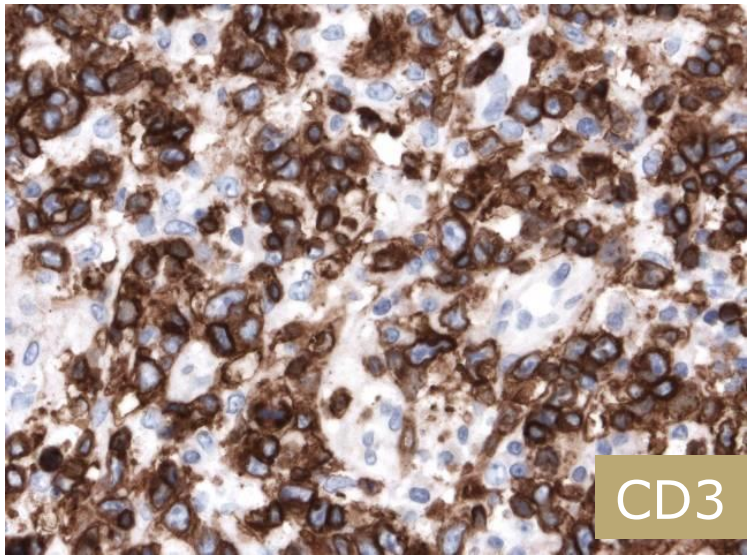
35 year-old woman from Kenya with cervical and axillary lymphadenopathy

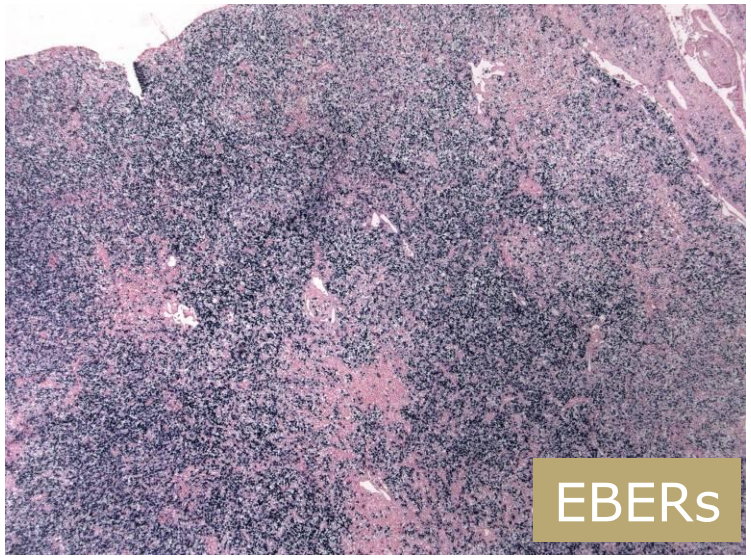


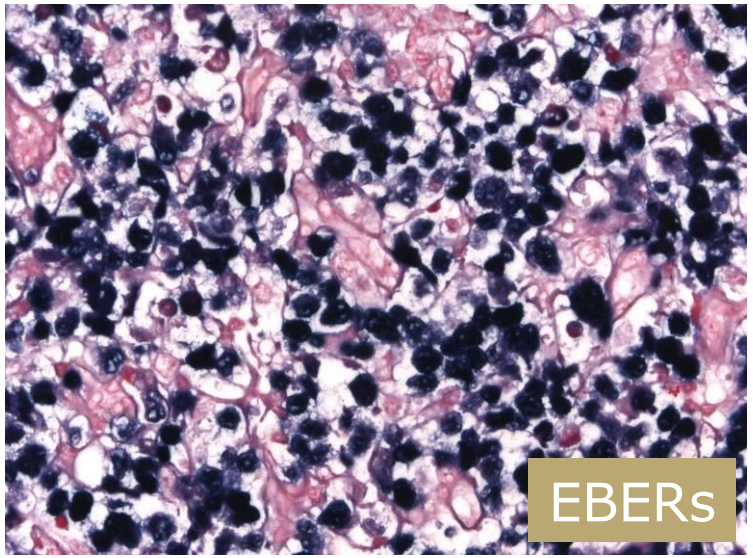


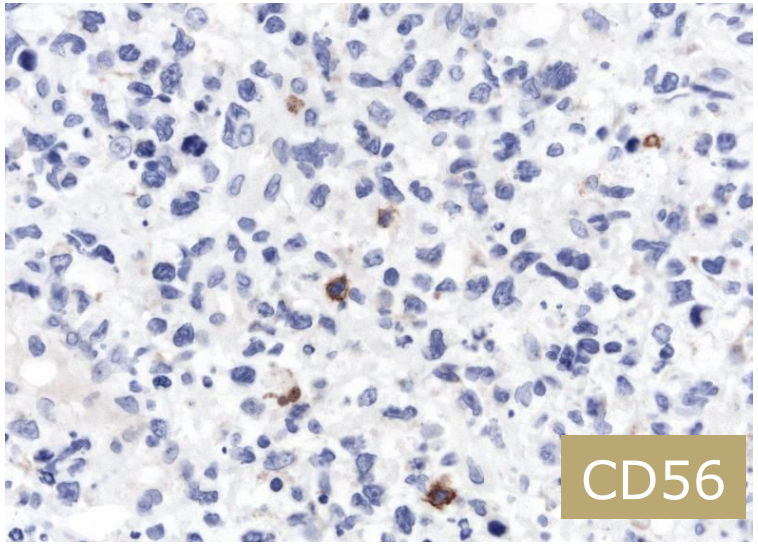


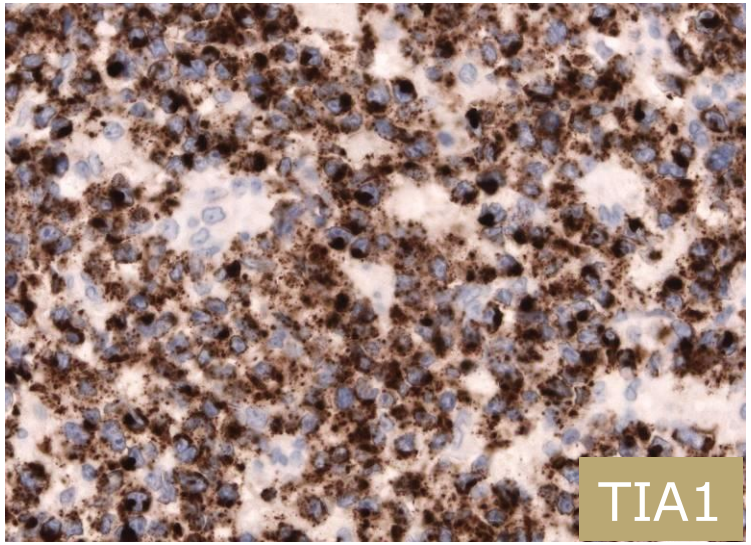
# Primary EBV+ nodal T or NK-cell lymphoma of γδ derivation

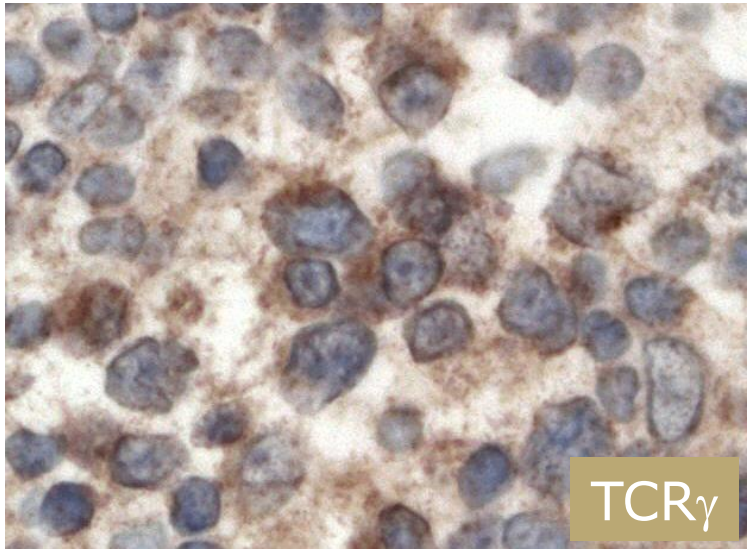


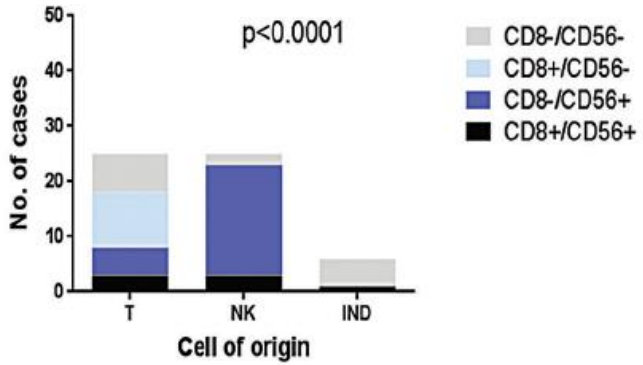



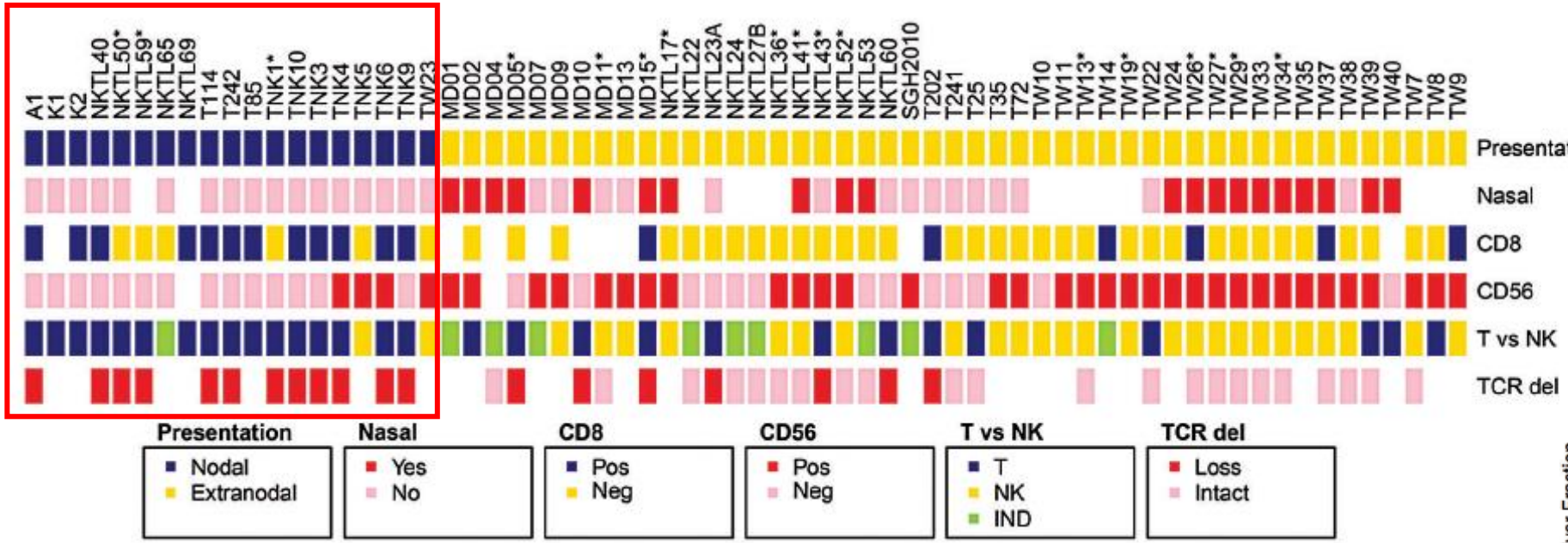



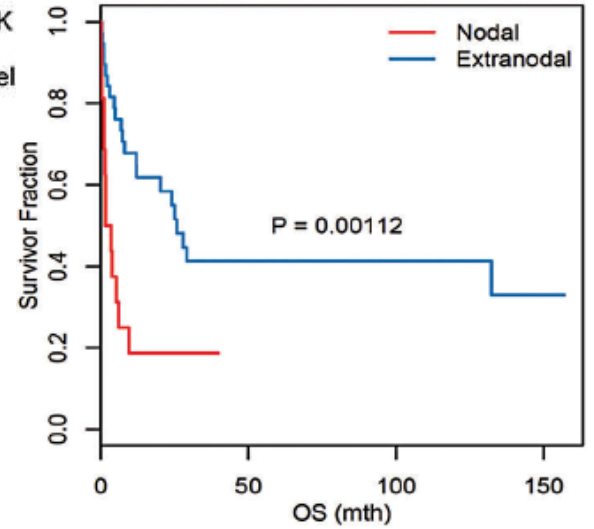



# Epstein-Barr virus-associated primary nodal T/NK-cell lymphoma shows a distinct molecular signature and copy number changes

Siok-Bian Ng,[1,2,3]* Tae-Hoon Chung,[3]* Seiichi Kato,[4] Shigeo Nakamura,[4] Emiko Takahashi,[5] Young-Hyeh Ko,[6] Joseph D. Khoury,[7] C. Cameron Yin,[7] Richie Soong,[1,3] Anand D. Jeyasekharan,[3] Michal Marek Hoppe,[3] Viknesvaran Selvarajan,[1] Soo-Yong Tan,[1,2] Soon-Thye Lim,[8] Choon-Kiat Ong,[9] Maarja-Liisa Nairismägi,[9] Priyanka Maheshwari,[2] Shoa-Nian Choo,[1] Shuangyi Fan,[1] Chi-Kuen Lee,[1] Shih-Sung Chuang[10] and Wee-Joo Chng[3,11]



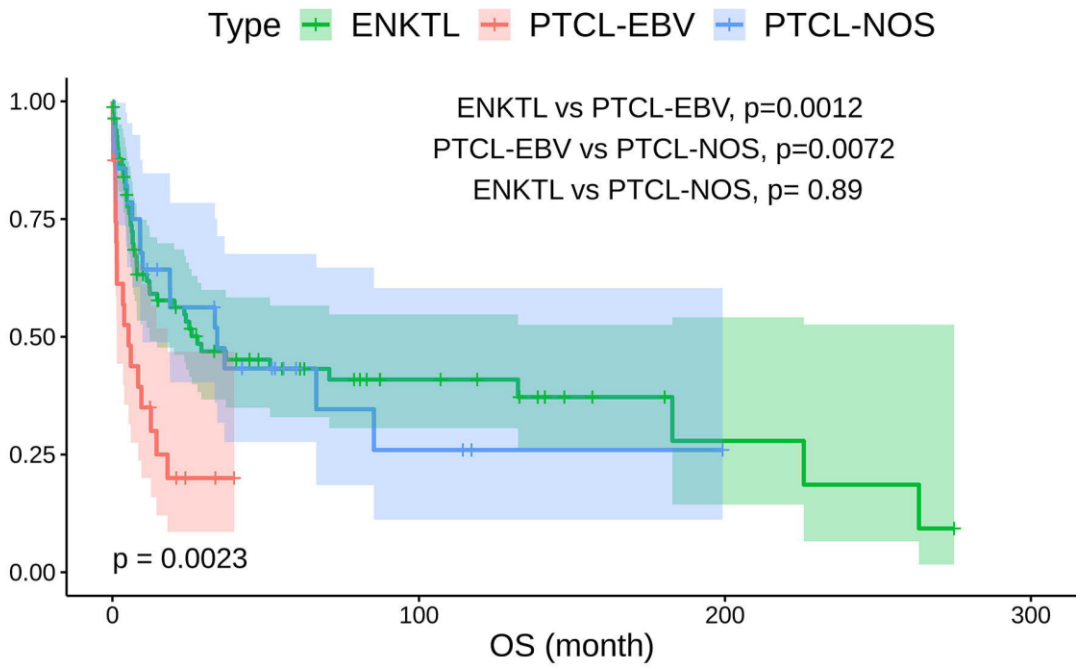



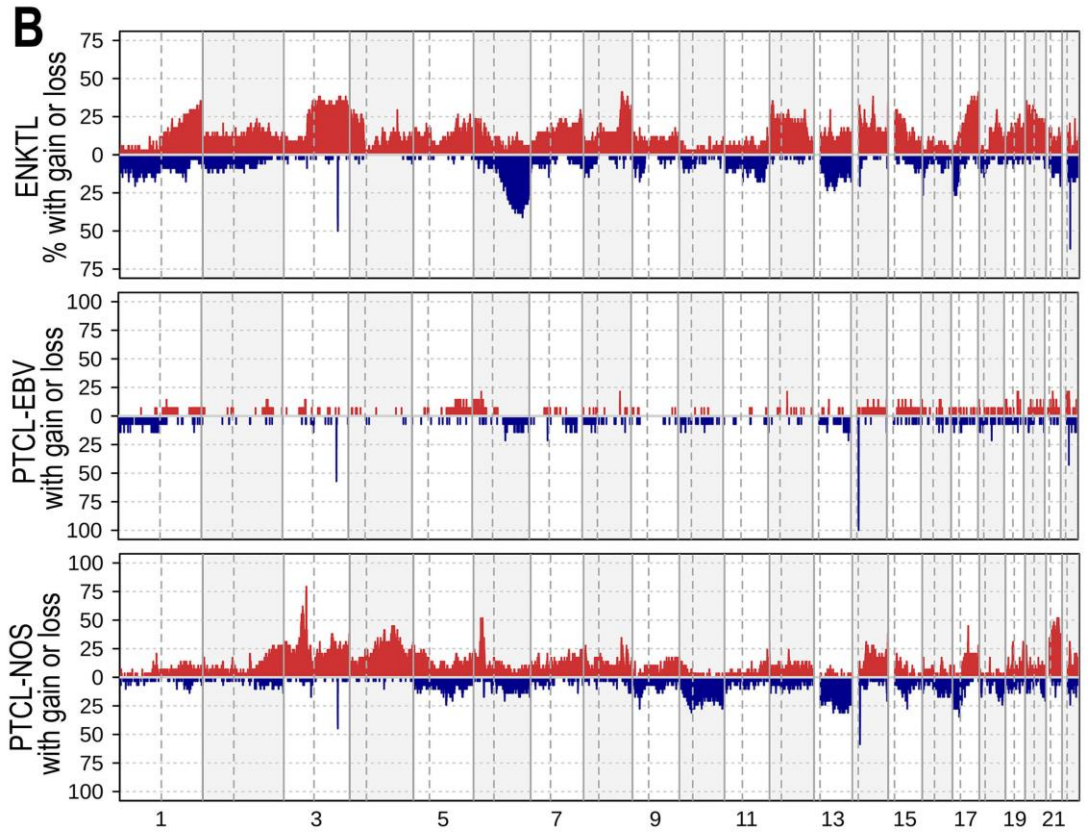




Nodal cases worse prognosis than extranodal cases

haematologica | 2018; 103(2)

# Primary EBV+ nodal T or NK-cell lymphoma




Low genomic instability

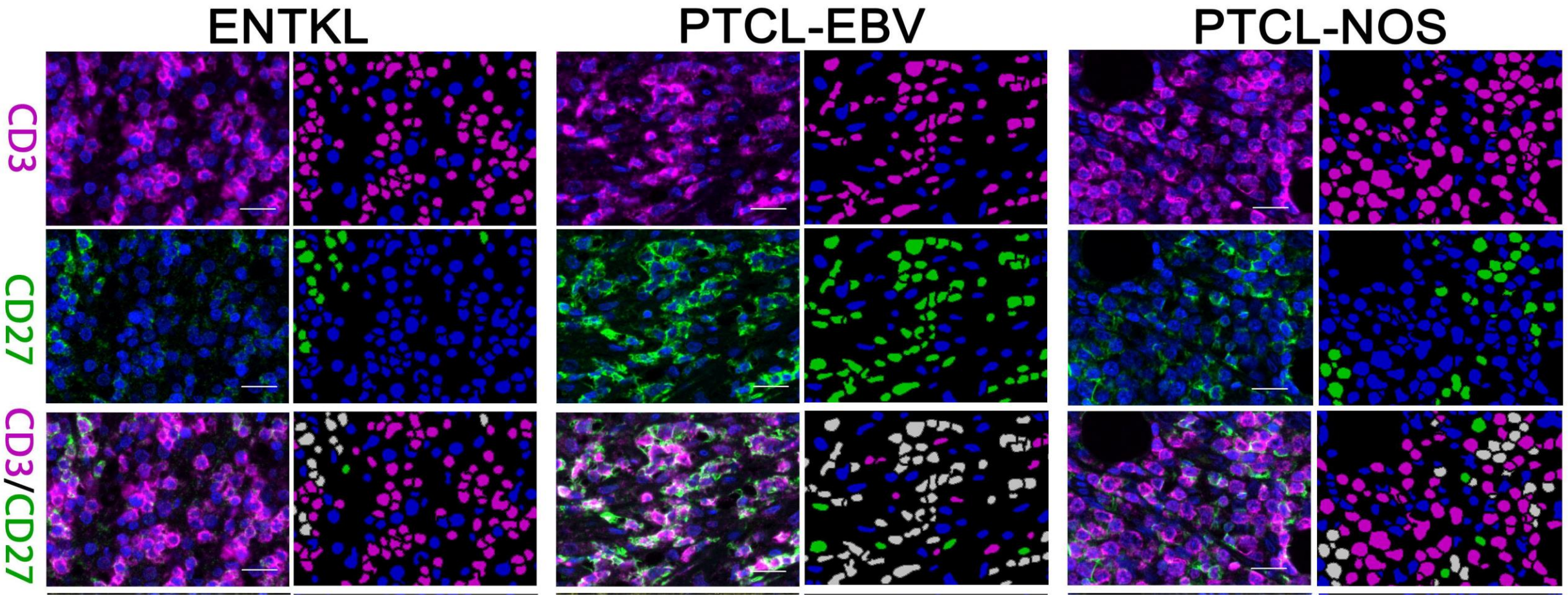
- Associated with older age
- Lack of nasal involvement
- CD8+/CD56- phenotype
- Frequent loss of 14q11.2 supporting the T-cell lineage
- Molecular signature with upregulation of PD-L1 and T-cell related genes

*Wai et al Haematologica 2022, Haematologica*

# EBV-associated T-and NK-cell LPD

- The better understanding of the EBV-associated LPDs has resulted on the recognition of well-defined entities and consequently improvement of their treatment
- The diagnosis of these disorders is complex and requires a multiparameter approach with complete clinical history
- NK disorders are rare
- Close collaboration with hematologists is very important

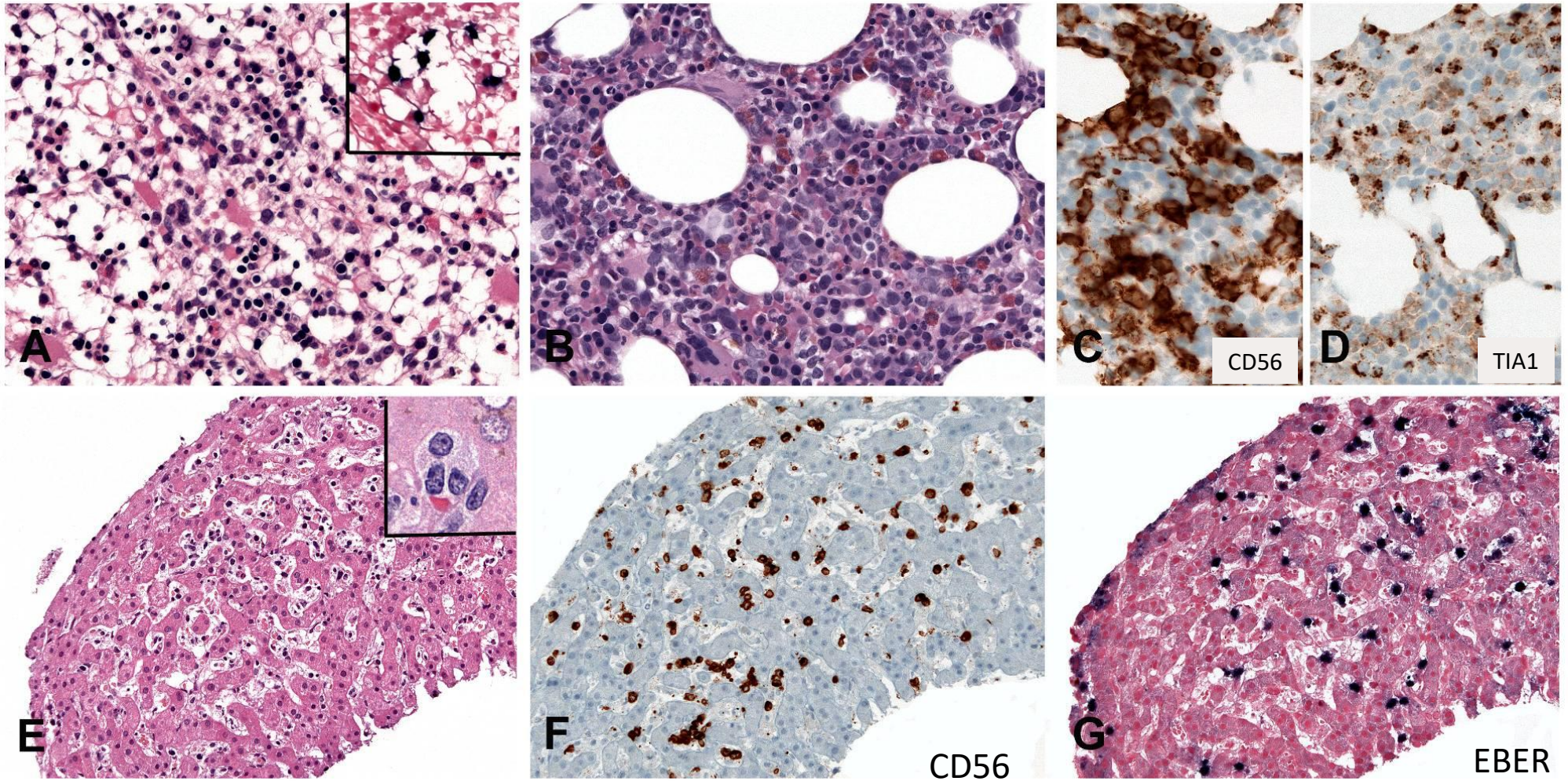
# NF-kB-associated genes, BIRC3, NFKB1 (p50) and CD27 are upreguated




Frequent mutations in *TET2, PIK3CD* and *STAT3*,
Upregulation of immune pathways
Downregulation of EBV miRNAS

*Wai et al Haematologica 2022, Haematologica*

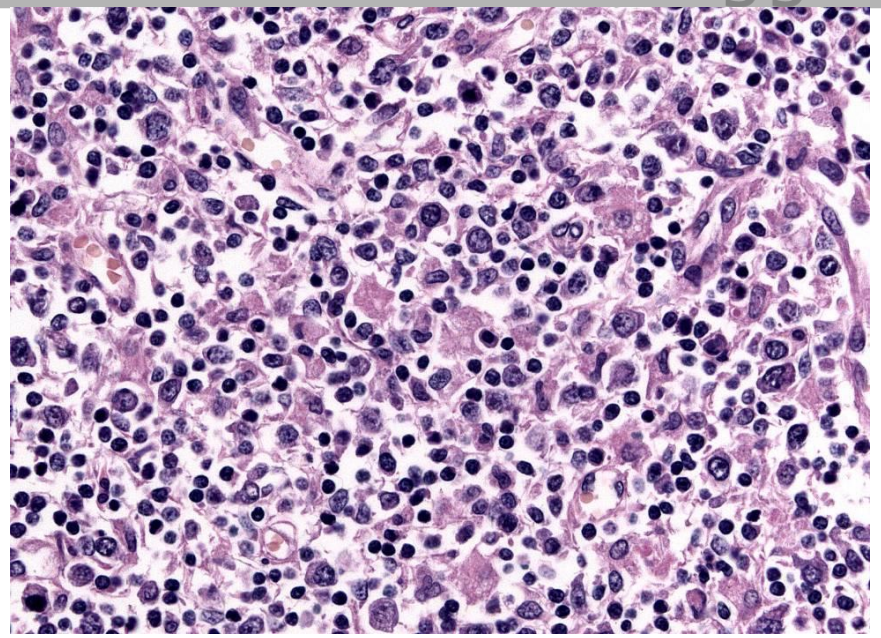
# Aggressive NK cell leukemia

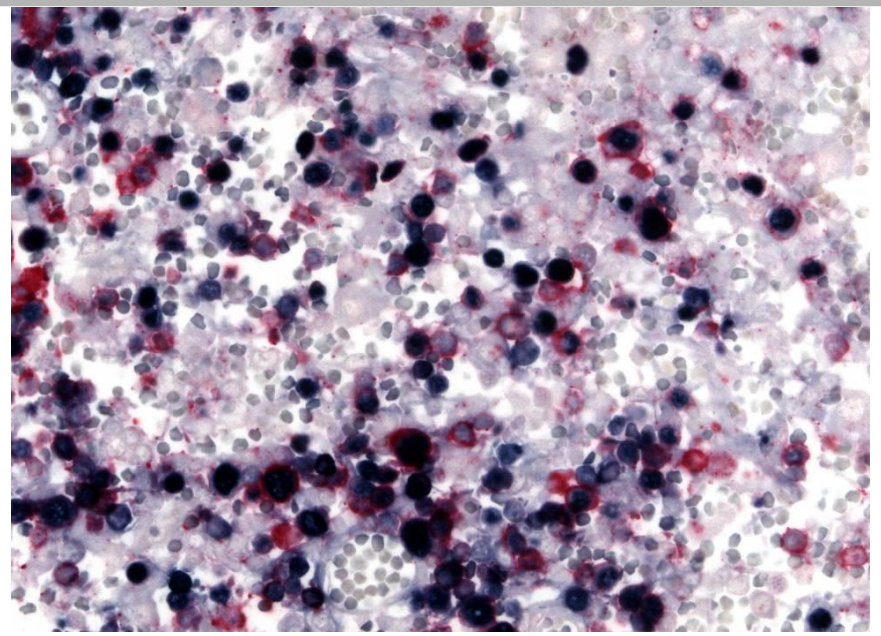



*Dojcinov, Fend, Quintanilla-Martinez, Pathogens 2018*

# Aggressive NK cell leukemia

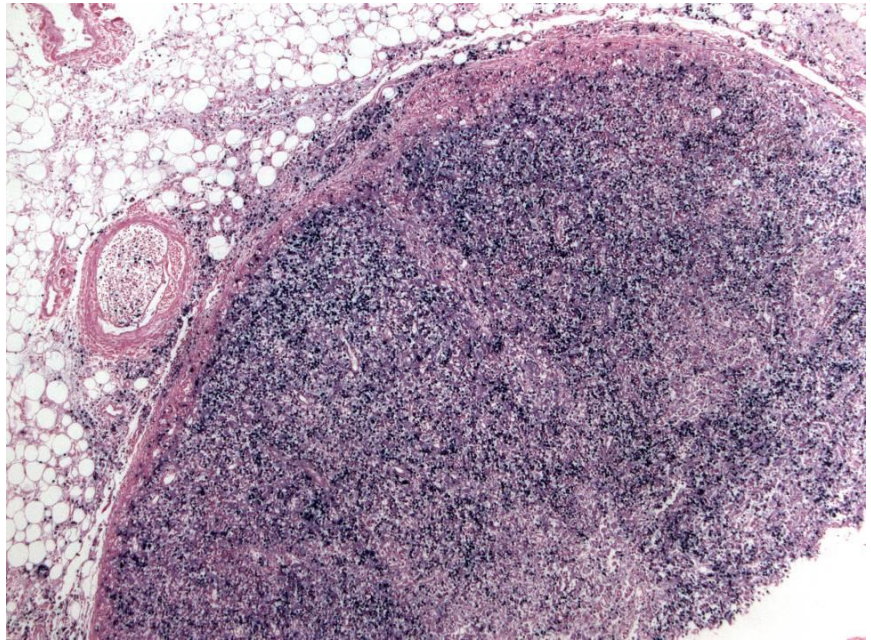
Spleen

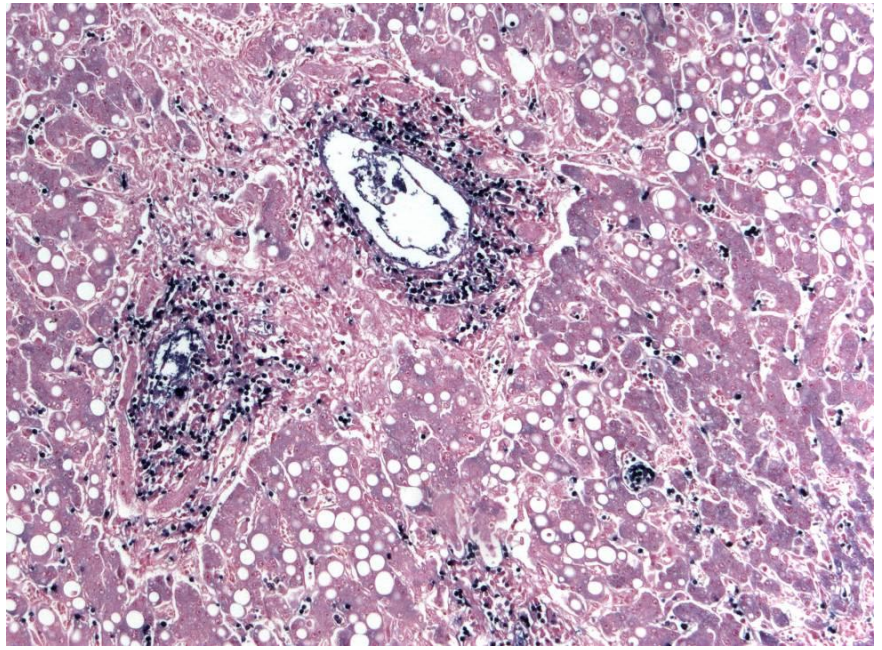




CD56/EBER

Lymph node





Liver