A very puzzling lymphoma case

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Case Report: 59-year old woman

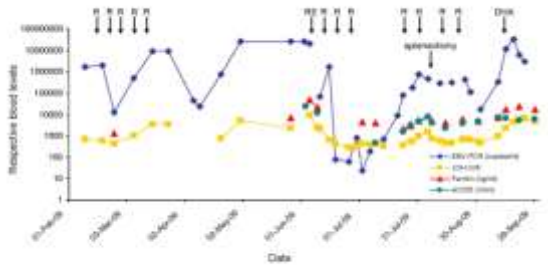
- 1995: Postinfectious dilated cardiomyopathy
- 1997: Orthotopic heart transplantation
- Initial triple immunosuppressive regimen with CSA, mycophenolate, and corticosteroids
- Monotherapy with CSA (80-100pg/µl plasma levels)
- Worsening of renal function
- Everolimus (4-8pg/µl), CSA (40-50pg/µl) to reduce CSA toxicity.

Case Report: 2009

- Recurrent fever, reduced general condition, urosepsis
- EBV-copies >1.6 million/ml
- LDH highly elevated
- CT: enlarged paracardial , retroperitoneal lymph nodes
- Clinical diagnosis: EBV-associated PTLD
- Reduction of CSA levels
- Rituximab (weekly doses of 375mg/m^2)

Case Report: May - July 2009

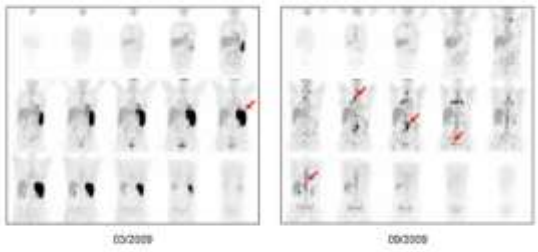
- Fever > 40°C, recurrent urosepsis
- Pancytopenia
- Hypertriglyceridemia
- High ferritin levels
- High soluble IL-2-receptor values (sCD25)
- EBV-copies > 26 million/ml
- Everolimus discontinued
- Etoposide (100mg/m2) for 3 days dexamethasone starting with 10mg/m2 and subsequent tapering over 2 weeks
- 2nd cycle of rituximab (375mg/m2 weekly for 4 weeks).



Time course of EBV copies and HLH parameters (LDH, Ferritin, s CD25) and response to therapy.

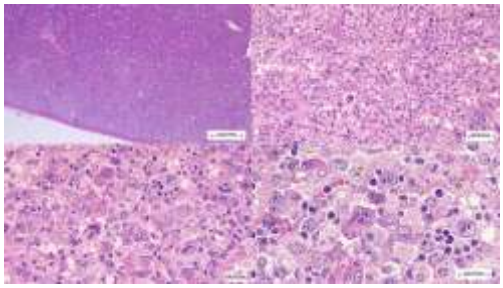
R: rituximab, RE: rituximab, etoposide, DHA: dexamethasone, cytarabine.

PET/CT: suspicious splenic hypermetabolism

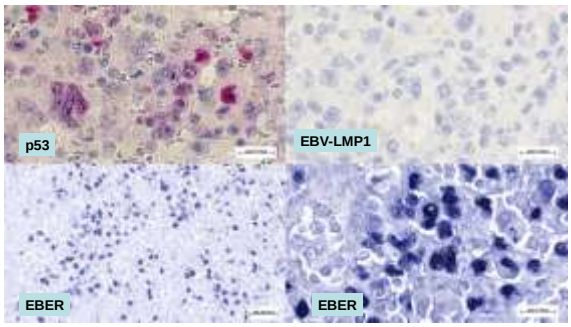


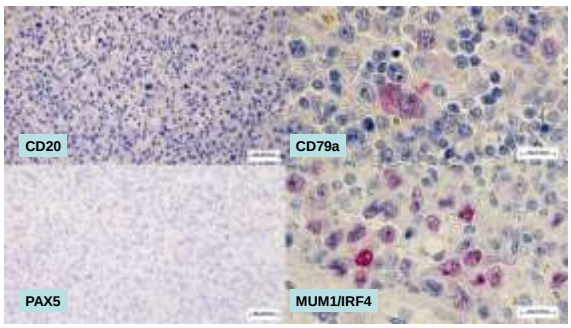
July 2009: Splenectomy (890g)

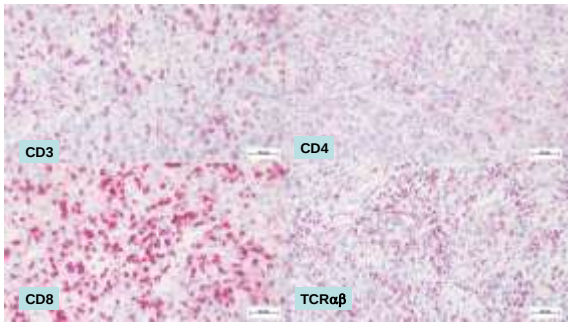
Spenectomy July 2009

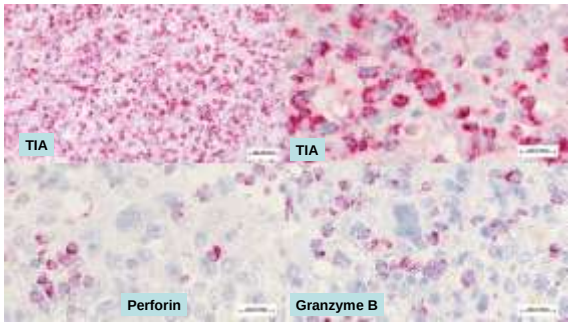


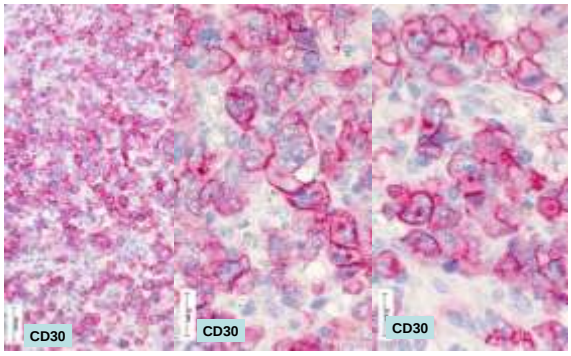
Spleen






CD3
CD4
CD8
TCRαβ

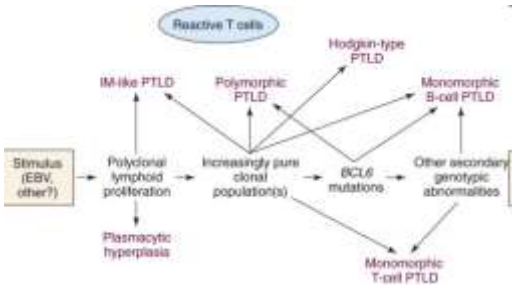

TIA
TIA
Perforin
Granzyme B


CD30
CD30
CD30

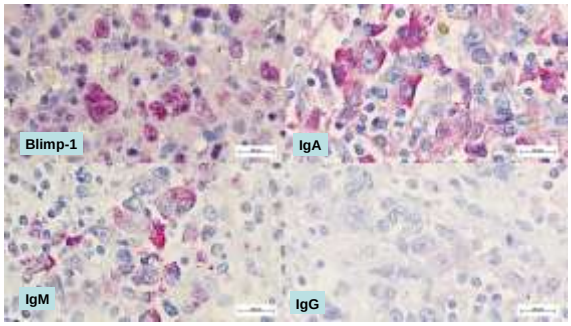
First proposed Diagnosis:

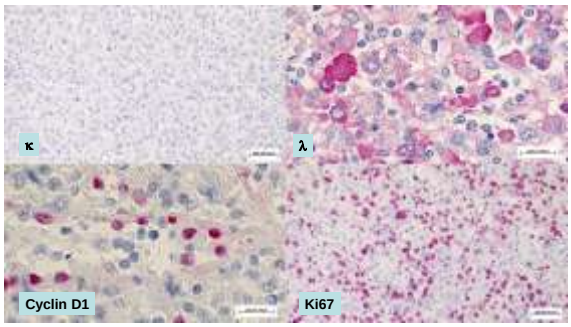
- **Late-onset post-transplant lymphoproliferative disorder (PTLD)**
- **EBV latency type III (LMP1 -, EBNA2-, ZEBRA-, EBER+)**
- **CD30+, TIA+, CD3-, CD4-, CD8-**
- **Monomorphic Tcell type, with features of anaplastic large cell lymphoma?**
- **TCR-γ: no rearrangement**

Model of PTLD



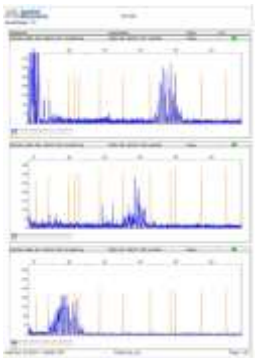
S. Swerdlow, F. Craig in E. Jaffe et al, Hematopathology 2010



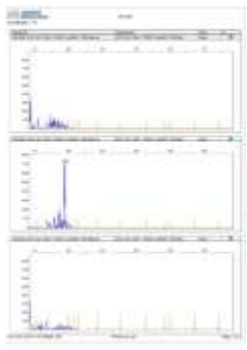


Final Diagnosis:

- **Late-onset post-transplant lymphoproliferative disorder (PTLD)**
- **EBV latency type III (LMP1 -, EBNA2-, ZEBRA-, EBER+)**
- **CD20- (Rituximab?), CD79a-/(+), MUM1/IRF4+,**
- **Blimp1+, CD38+/-, Lambda+, IgA+, IgM+/-,**
- **CD30+, TIA+**
- **Monomorphic B-cell PTLD with features of a plasmablastic lymphoma**

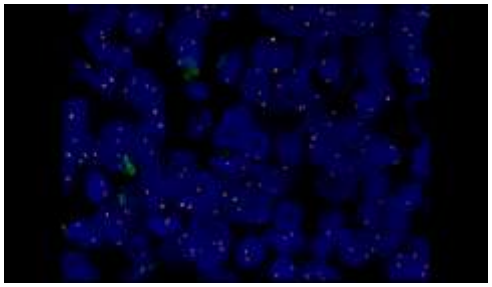


IgH PCR (biomed2 Primer)

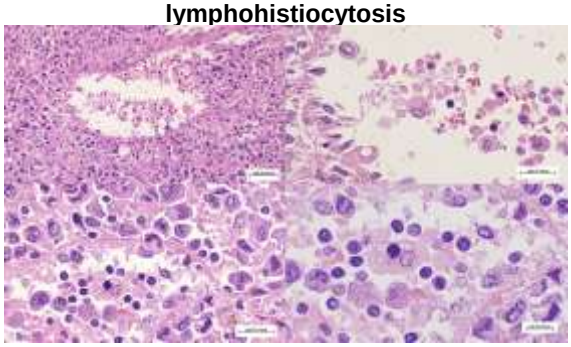


IgH FR3 MUT JH3

FISH bap: cMyc-, BCL6-, BCL2-, ALK-



Evidence of hemophagocytic lymphohistiocytosis



Case Report: post-splenctomy

- **Hemoglobin and platelets normalized**
- **The patient was discharged in still reduced, but stable condition, 2 weeks later: readmission**
- **EBV-copies rising**
- **i. v. antiviral therapy with foscarnet**
- **dexamethasone 40 mg,cytarabine 2 x 2 g/m² following the DHA protocol, neutropenia**
- **broad-spectrum antibiotic, antiviral and antifungal therapy**
- **Death 9 months after onset of PTLD**

Diagnostic criteria of HLH

- **Clinical criteria: Fever, Splenomegaly**
- **Laboratory criteria**

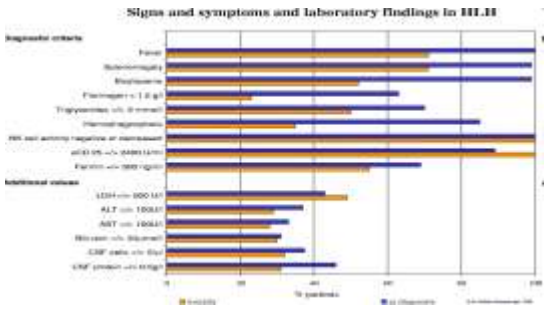
  Cytopenia (at least 2 cell lines): hemoglobin < 9 g/l (below 4 weeks < 120 g/l), platelets <100 x10^9/l, neutr. <1x10^9/l

  Hypertriglyceridemia (Fasting triglycerides > 3 mmol/l) and / or hypofibrinogenemia (Fibrinogen < 1.5 g/l)

  Ferritin > 500 µg/l

  sCD25 (sIL-2) > 2400 U/ml,

  Decreased or absent NK-cell activity
- **Histopathological criteria**
- **Hemophagocytosis in bone marrow, lymph node, spleen or liver**

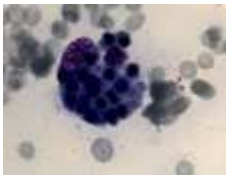


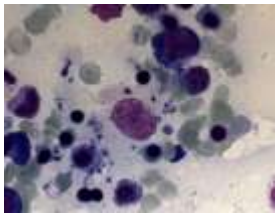
European Journal of Pediatrics© Springer-Verlag 200610.1007/s00431-006-0258-1**Review**
Familial and acquired hemophagocytic lymphohistiocytosis
Gritta E. Janka1, 2 ,

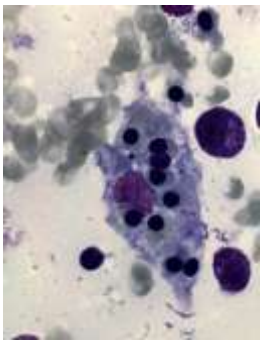
Case 2: 21-year old female student

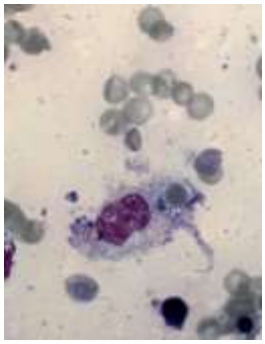
presenting with sudden onset of fever, pancytopenia and increased serum ferritin and transaminases.

Bone marrow aspirate

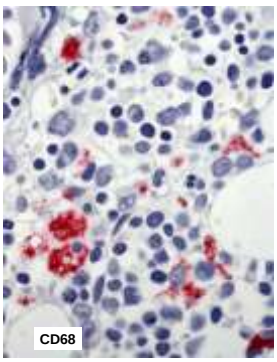


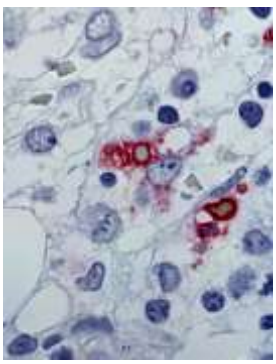


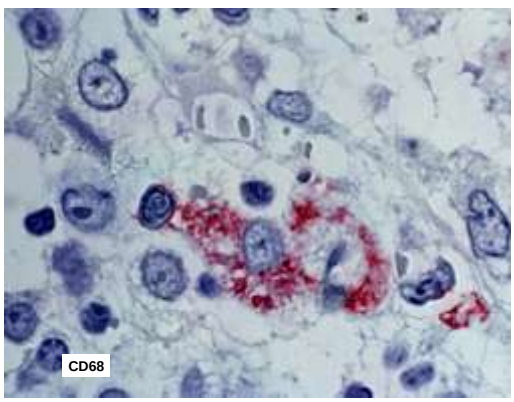


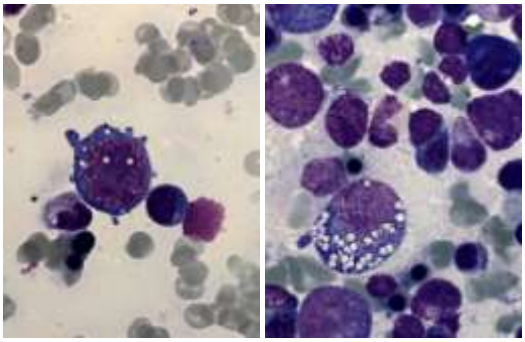


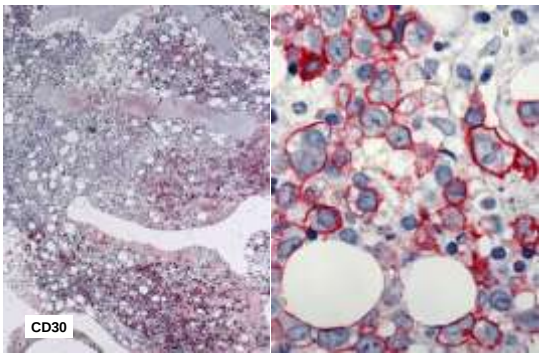
Bone marrow trephine biopsy









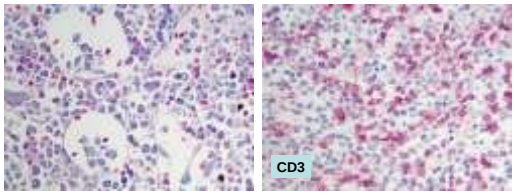


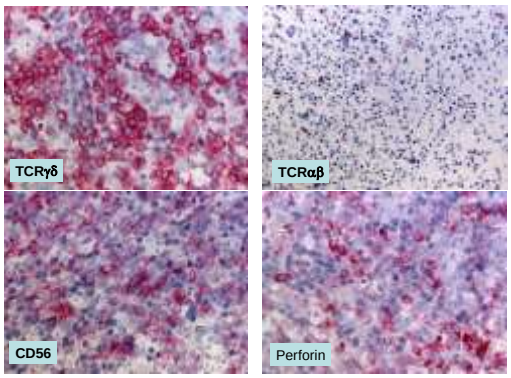
Diagnosis

- **Anaplastic large cell lymphoma, ALK- complicated by HLH**
- **The patient succumbed rapidly to multi organ failure due to HLH**

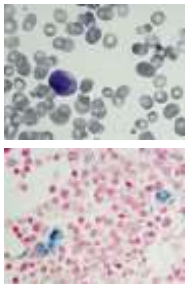
Case 3: 32-year old male patient Wegener's disease, cANCA +

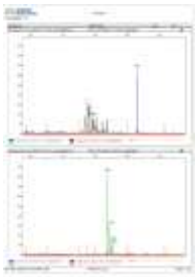
Fever, Splenomegaly, Pancytopenia: Bone marrow trephine biopsy





Hepatosplenic γδ T-Cell Lymphoma





TCR Gamma PCR

Classification of HLH

Acquired HLH

- **Exogeneous agents:** infections, toxins
  - Infection-associated hemophagocytic syndrome (IAHS)

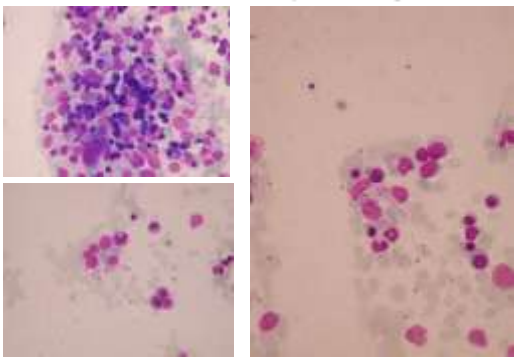
  Endogenous products: tissue damage, metabolic products

  Rheumatic diseases: macrophage activation syndrome (MAS)

  Malignant diseases: Malignant endodermal sinus tumor associated with fatal hemophagocytic syndrome

Chaudary IU, Bojal SA, Attia, A, Al-Dossary B, Al Dayel AQ, Amr SS . Hematol Oncol Stem Cell Ther 2011; 4: 138-14

Leishmaniasis complicated by HLH



Classification of HLH

Genetic HLH

- **Familial HLH (Farquhar disease)**
  - Known gene defects, unknown gene defects
- **Immune deficiency syndromes with albinism**
  - Chédiak-Higashi syndrome 1
  - Griscelli syndrome 2
  - X-linked lymphoproliferative syndrome

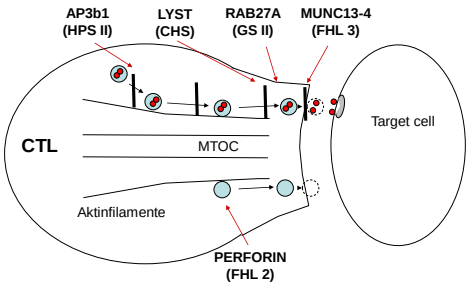
GJ Janka, 2007

Classification of HLH

- **Genetic disorders with predisposition for HLH:**
  - **FHL-2 (*perforin*)**
  - **FHL-4 (*syntaxin 11*)**
  - **FHL-3 (*munc 13-4*)**
  - **XLP (*sap*)**

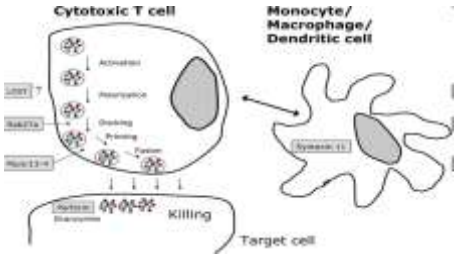
S. Ehl, 2011

Defect of cytotoxicity



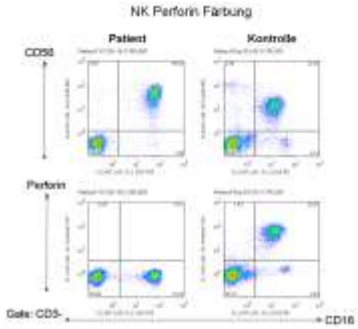
Modified from de Saint Basile, Curr Opin Rheumatol. 2003, 15:436

HLH

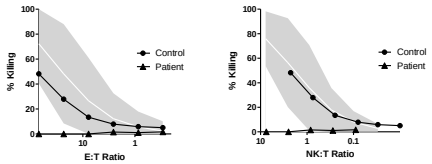


Modified from de Saint Basile, Curr Opin Rheumatol. 2003, 15:436

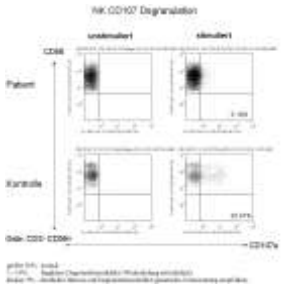
Perforin deficiency

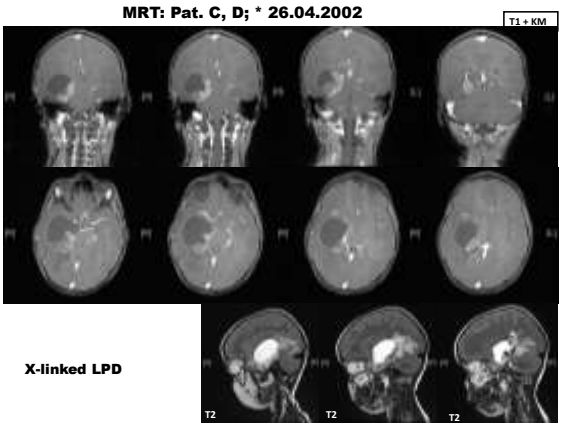


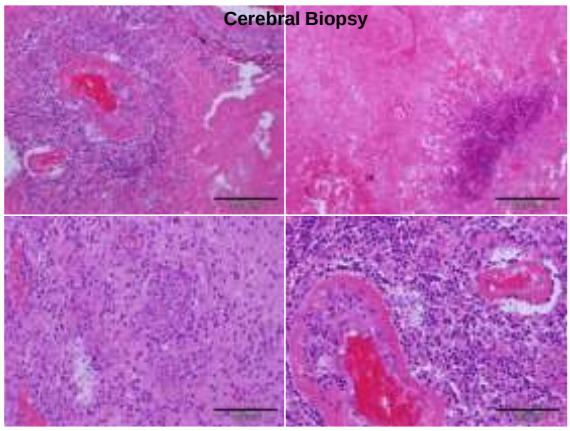
NK cytotoxicity in Perforin Mutation

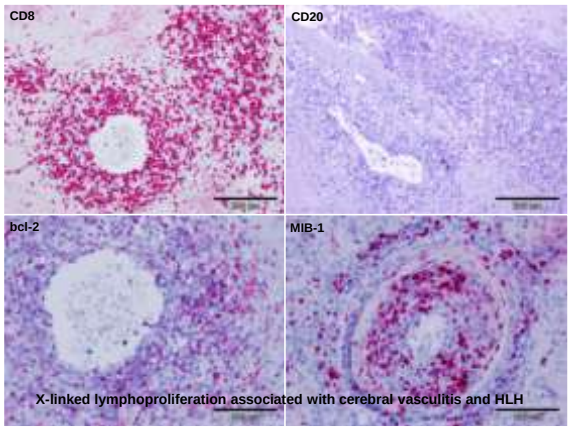


NK Degranulation in Munc13-4 Mutation

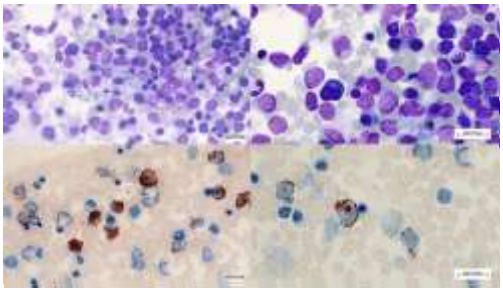



MRT: Pat. C, D; * 26.04.2002
T1 + KM
X-linked LPD
T2
T2
T2

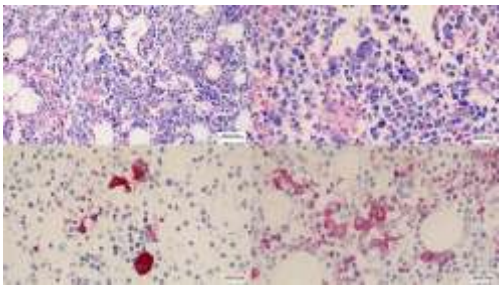

Cerebral Biopsy


CD8
CD20
bcl-2
MIB-1
X-linked lymphoproliferation associated with cerebral vasculitis and HLH

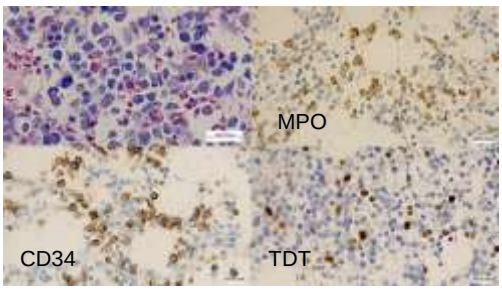
Acute myeloid leukemia secondary to Fanconi's anemia

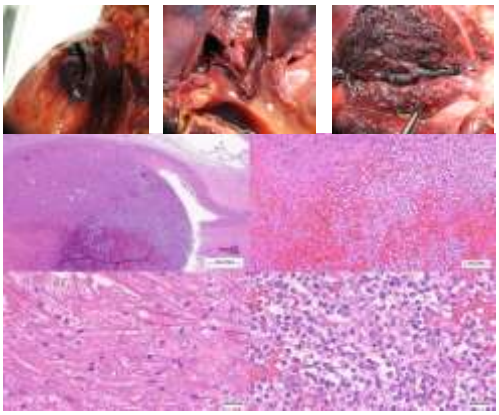


AML with MDS-related changes

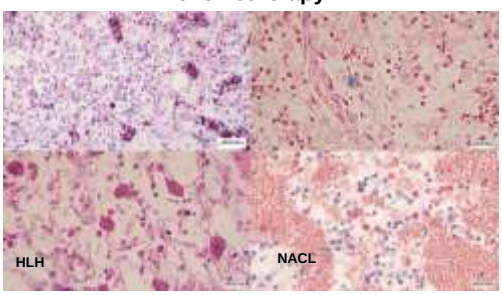


AML with MDS-related changes

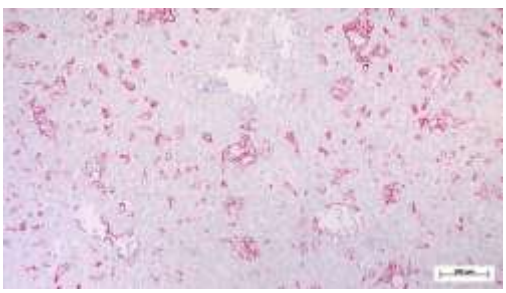




At Autopsy: Heamophagocytosis associated with marked marrow hypoplasia without chemotherapy



HLH in animal models: Kupffer cell activation in the liver



Jessen,.....Schmitt-Graeff, ..Ehl, Blood 2011)

HLH: Perspectives

- HLH-94 treatment protocol: Immunosuppressive and cytotoxic therapy aiming at clinical remission (etoposide in combination with dexamethasone, intrathecal metotrexate in patients with neurologic symptoms)
- HSCT in patients with familial, progressive or persistent disease
- 5-year survival 66%, in FHLH 50% (non survived without HSCT).
- Considerably improved outcome

Trottestam et al., Blood 2011: 118: 4577

Haemophagocytic lymphohistiocytosis (HLH)

- Life-threatening condition of severe hyperinflammation
- Uncontrolled proliferation of activated lymphocytes and histiocytes
- Secretion of high amounts of inflammatory cytokines
- Impaired NK and cytotoxic T-cell function shared by all forms of HLH
- Awareness of clinical symptoms and diagnostic criteria is crucial to start life-saving therapy in time

G E Janka, Eur J Pediatr 2007; 166: 95-109

Acknowledgments

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University Hospital Hamburg, Germany