European Reference Network
for rare or low prevalence complex diseases

Network Paediatric Cancer (ERN PaedCan)

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Triin Pohlak & Birgit Burkhardt

A challenging case of generalised precursor B-cell lymphoblastic lymphoma (pre-B-LBL) in an infant

Moderation: Raheel Altaf Raja

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SIOPE YOUNG

St. Anna Kinderkrebs Forschung

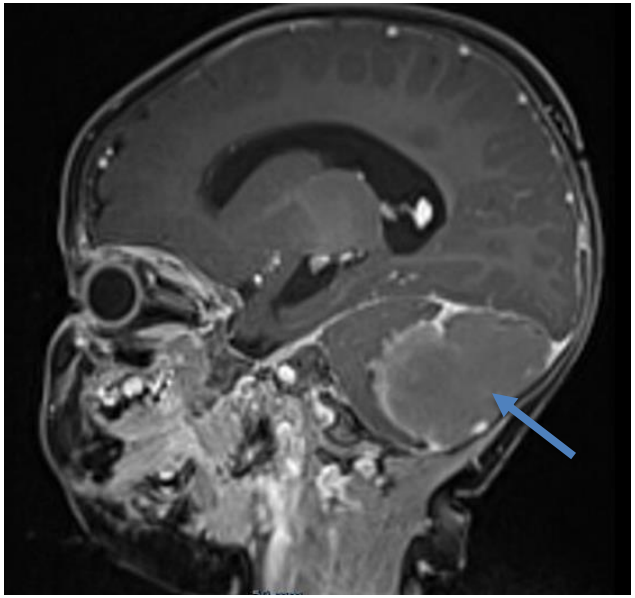
COI declaration

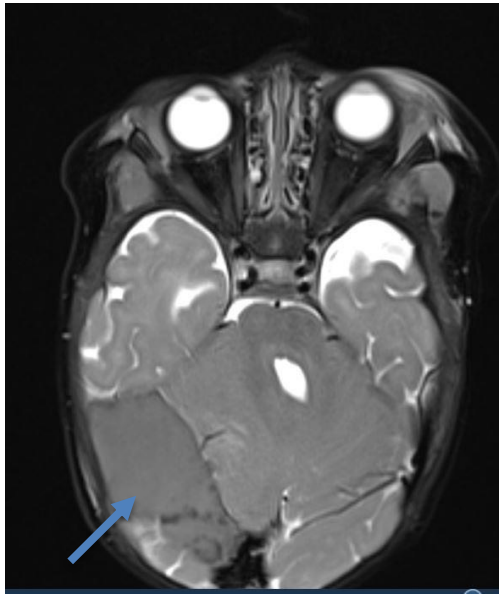
- Dr Pohlak
  - has received travel funding from Roche (not relevant regarding this presentation)
- Dr Burkhardt
  - no conflict of interest

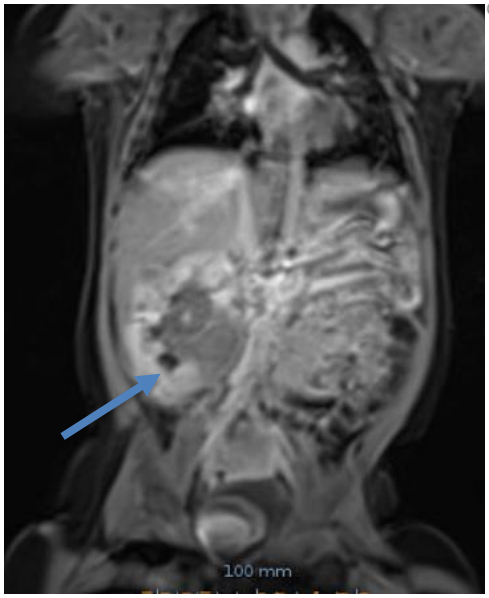
Case description

- Patient – 7 months old girl
- Swelling around the eyes (left>right) and cheeks
  - Allergic reaction?
  - Infection? Facial cellulitis?
  - No improvement with antibiotics and antihistamines
- Gradually worsening lethargy; seldom vomiting
- Opisthotonus, no meningeal symptoms

Radiology

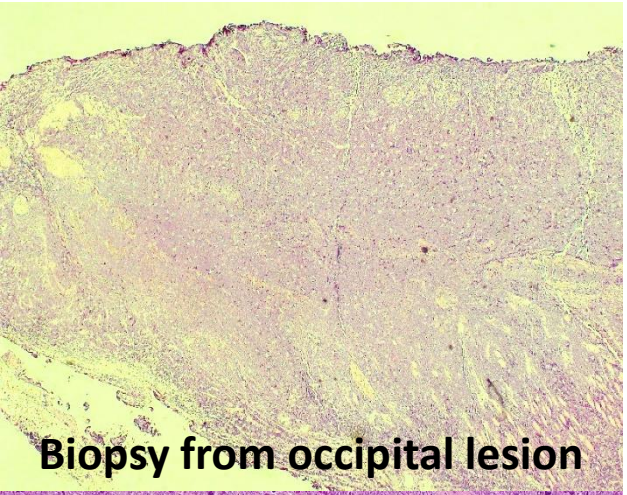


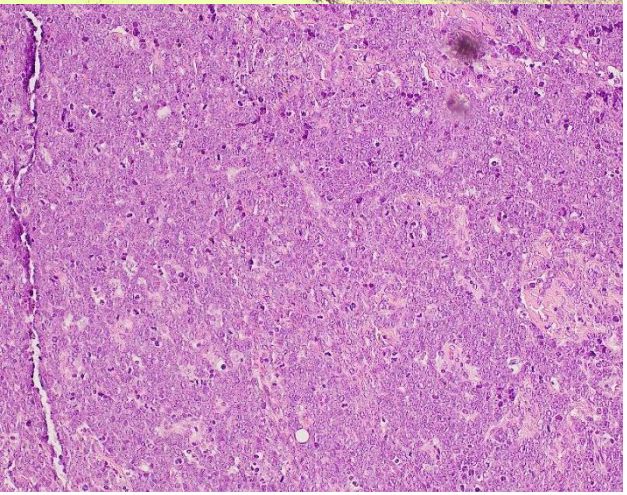


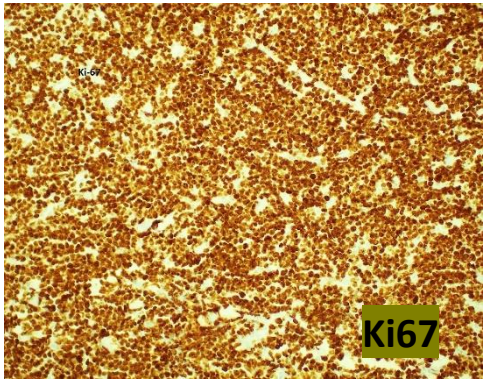


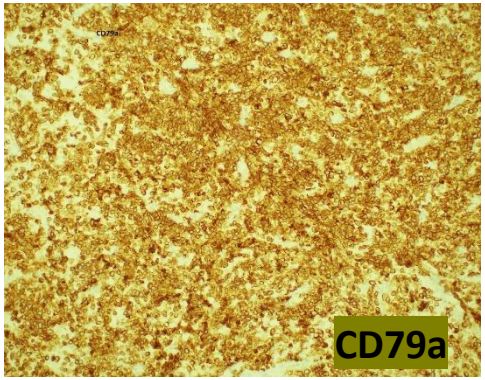
- Ultrasound: possible abscess
- **MRI**
  - Generalised malignant process, with tumour involvement in both kidneys, head and facial region (soft tissues and bones), intracranium (posterior fossa), retroperitoneum, pelvic bones, spine, L4 spinal canal
  - Primary tumour – right kidney?

Histology









Immunohistochemistry: CD45+, CD20-, BSAP+, CD79a+, CD10+, TdT+, CD34-, MPO-, CD33-, CD3-, CD7-, CK AE1/AE3-, WT1-, CK8/18, CD56-

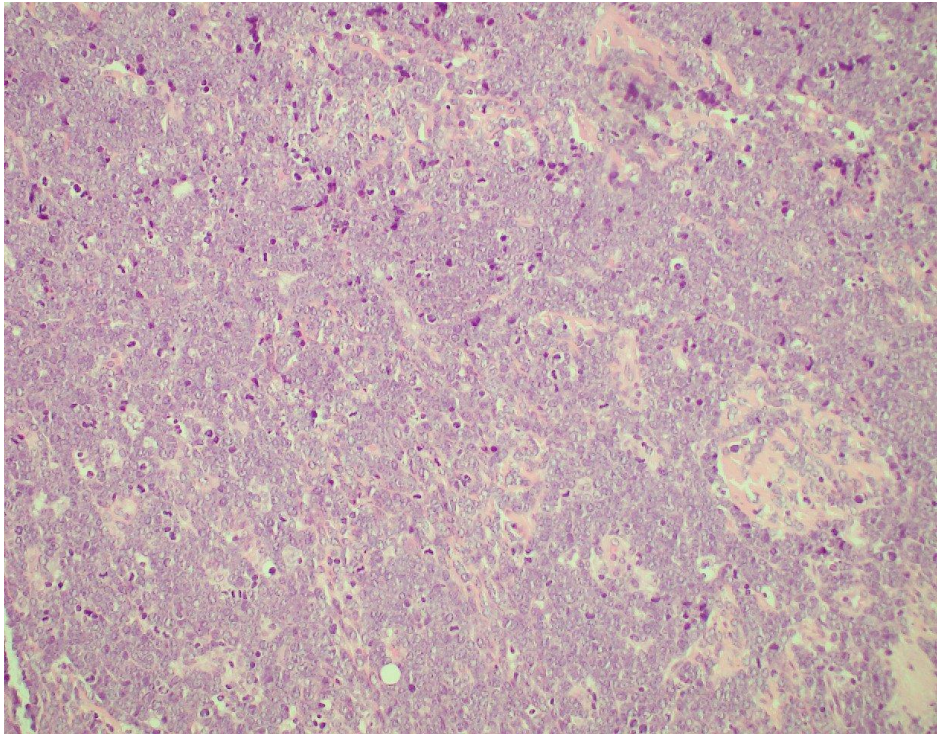
Cerebrospinal fluid (from external drainage) negative

Bone marrow aspirate

Morphology: mainly normal, a few (up to 1%) blasts

Flow cytometry: ~0,17% cells with following phenotype: CD45+, CD19+, CD10+, CD38+, cy79a+, TdT-, CD20-, CD33-, CD7-, CD34-, CD117-

Diagnosis



Precursor B lymphoblastic lymphoma

(pre-B-LBL)

Question 1

What is the stage of the disease?

a) I

b) II

c) III

d) IV

International Pediatric Non-Hodgkin Lymphoma Staging System	
Stage	Criteria for extent of disease
I	A single tumor with exclusion of mediastinum and abdomen
II	A single tumor with regional node involvement ≥ 2 nodal areas on the same side of the diaphragm A primary gastrointestinal tract tumor (usually in the ileocecal area), with or without involvement of associated mesenteric nodes, that is completely resectable (if malignant ascites or extension of tumor to adjacent organs, it should be regarded as stage III)
III	≥ 2 extranodal tumors (including EN-B or EN-S) above and/or below the diaphragm ≥ 2 nodal tumors above and below the diaphragm Any intrathoracic tumor (mediastinal, hilar, pulmonary, pleural, or thymic) Intra-abdominal and retroperitoneal disease, including liver, spleen, kidney, and/or ovary localizations, regardless of degree of resection (except primary gastrointestinal tract tumor [usually in ileocecal region] and/or involvement of associated mesenteric nodes that is completely resectable) Any paraspinal or epidural tumor, regardless of whether other sites are involved A single bone lesion with concomitant involvement of extranodal and/or non-regional nodal sides
IV	Any of the above findings with Initial involvement of CNS (stage IV CNS) Initial involvement of the bone marrow (stage IV BM) Initial involvement of CNS and bone marrow (stage IV combined) based on conventional methods

Treatment

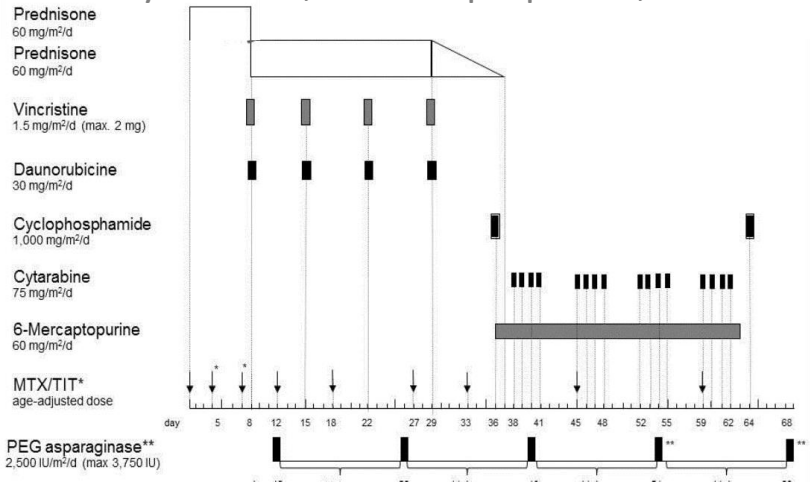
- According to LBL-2018 protocol
  - **Prephase:** prednisolone
  - **Induction:** prednisolone, vincristine, daunorubicine, PEG asparaginase, intrathecal triple therapy
  - **Consolidation:** PEG asparaginase, cyclophosphamide, cytarabine, 6-mercaptopurine, intrathecal triple therapy

High risk group

T-LBL N/F^{WT}

pB-LBL stage III/IV

all CNS positive patients

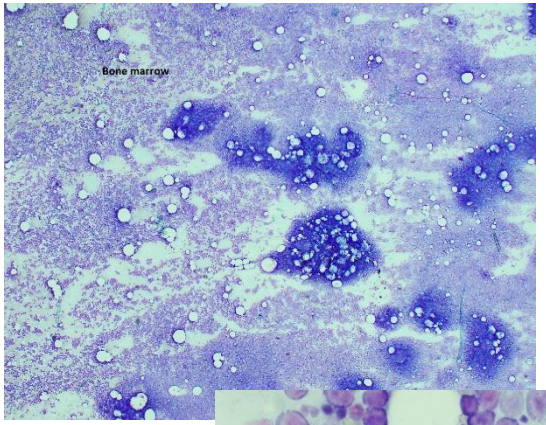


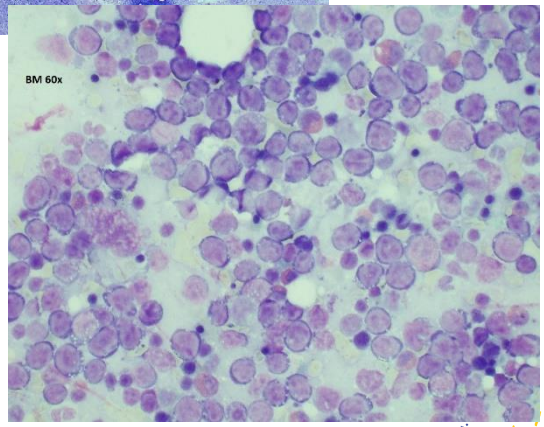
- FDG-PET negative ~2 months after start of treatment – no metabolic activity in the tumour, Deauville 1
- CSF negative for lymphoma cells

1st relapse

5 months after primary diagnosis (age 1 year)

- Peripheral blood: LDH ↑↑, leukocytosis and eosinophilia, ~1% blasts
- **Bone marrow aspirate**
  - Morphology: 50-55% malignant infiltrate
  - Flow cytometry: ~29% blasts with initial phenotype
  - FISH: t(8;14) MYC-IGH (with atypical signals) positive
- **Cerebrospinal fluid (CSF)**
  - Flow cytometry: no CD19+ cells, no lymphoma cells detected
- Review of primary biopsy and consultations with external experts confirmed the diagnosis





Question 2

Is it leukaemia or lymphoma?

a) Leukaemia

b) Lymphoma

Treatment (2)

- ICE regimen (ifosfamide, carboplatin, etoposide) x2
- Achieved remission after 1st course:
  - FDG-PET negative (Deauville 1)
  - Bone marrow hypoplastic, no blastosis

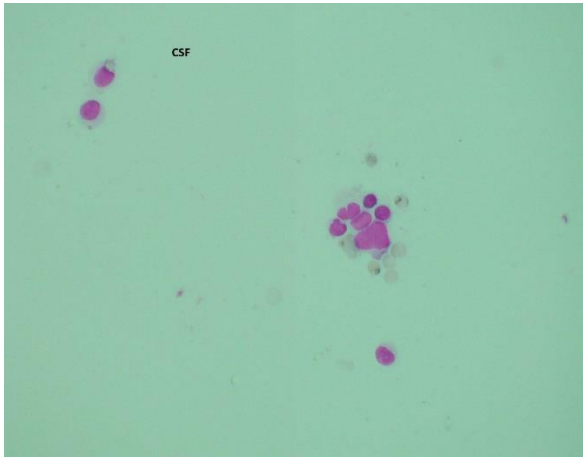
- Problems: severe mucositis, sepsis, long-term bone marrow hypoplasia

2nd relapse

2,5 months after 1st relapse (age 1 year 2 months)

- **Bone marrow aspirate**
  - Morphology: 15-25% malignant infiltrate
  - Flow cytometry: ~12% blasts with initial phenotype (CD19+, CD10+, CD20 heterog, CD34-, CD38+)

- **CSF**
  - Cytology: 13% lymphoblasts
  - Flow cytometry: 57% blasts with initial phenotype (CD19+, CD45+/dim, CD10+, CD22+/dim, CD20-, CD3-, CD14-)



Treatment (3)

- IntReALL protocol HIB block
  - Dexamethasone, vincristine, mitoxantrone, PEG-Asparaginase, bortezomib + intrathecal triple therapy
- Achieved remission (both BM and CSF)
- Problems: bone marrow aplasia, sepsis, ileus (required ICU)

B-WBC:	0,39
B-RBC:	2,3
B-Hb:	66
B-Hct:	19,9
B-MCV:	86,5
B-MCH:	28,7
B-MCHC:	332
B-PLT:	67
B-Diff-LYMPH-%:	30,8
B-Diff-NEUT-%:	61,5
B-Diff-Mono-%:	7,7
B-Diff-Eo-%:	0
B-Diff-Baso-%:	0
IG%:	0
B-Diff-LYMPH-arv:	0,12
B-Diff-NEUT-arv:	0,24
B-Diff-Mono-arv:	0,03
B-Diff-Eo-arv:	0

Question 3

If you considered an immunotherapy, what would you choose?

a) Inotuzumab ozogamicin
b) Blinatumomab
c) CAR-T therapy
d) Rituximab
e) Something else

Treatment (4)

- Blinatumomab (anti-CD19 bispecific T-cell engager)

- Haploidentical haematopoietic stem cell transplantation
  - 10 months after primary diagnosis
  - Donor: mother; 6/12 HLA match; both CMV positive
  - BuFluTT+ATG conditioning

Outcome

- Patient is 3,5 years old now and has stayed in remission +2 years post-HSCT, complete donor chimerism

- Problems:
  - CMV reactivation (treatment with valganciclovir and ganciclovir)
  - Recurrent upper respiratory infections
  - Osteopenia with spontaneous fractures

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DISCUSSION

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Take home messages

- **Think outside the box**
  - There isn't always one right way to treat challenging cases
  - Sometimes off-label novel treatment options are needed

- Even when the malignancy is in remission, persistent health problems may remain