Diagnosis and treatment of FHL - first patient with complete perforin deficiency diagnosed in Czech Republic

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Introduction

HLH – uncontrolled proliferation of T lymphocytes and macrophages

- familial (primary) hemophagocytic lymphohistiocytosis (FHL)
- secondary HLH (systemic infection, malignancy or syst. AI)

FHL – fatal inherited disease of infancy and early childhood
1:50 000 live born

- the only chance for cure – allo stem cell transplantation (SCT)

- 30% patients – mutation in perforin gene (10q21.3-22)
perforin deficiency in T-lymphocytes and NK cells

- defect in NK and Tcells cytotoxicity

Family and past medical history

- girl, 1 month old at diagnosis of FHL

FH: negative

PMH: from 2nd pregnancy

delivery in 38th week, 2750g/47 cm,
adaptation after delivery normal

- first 4 weeks of life without complications

Onset of the disease

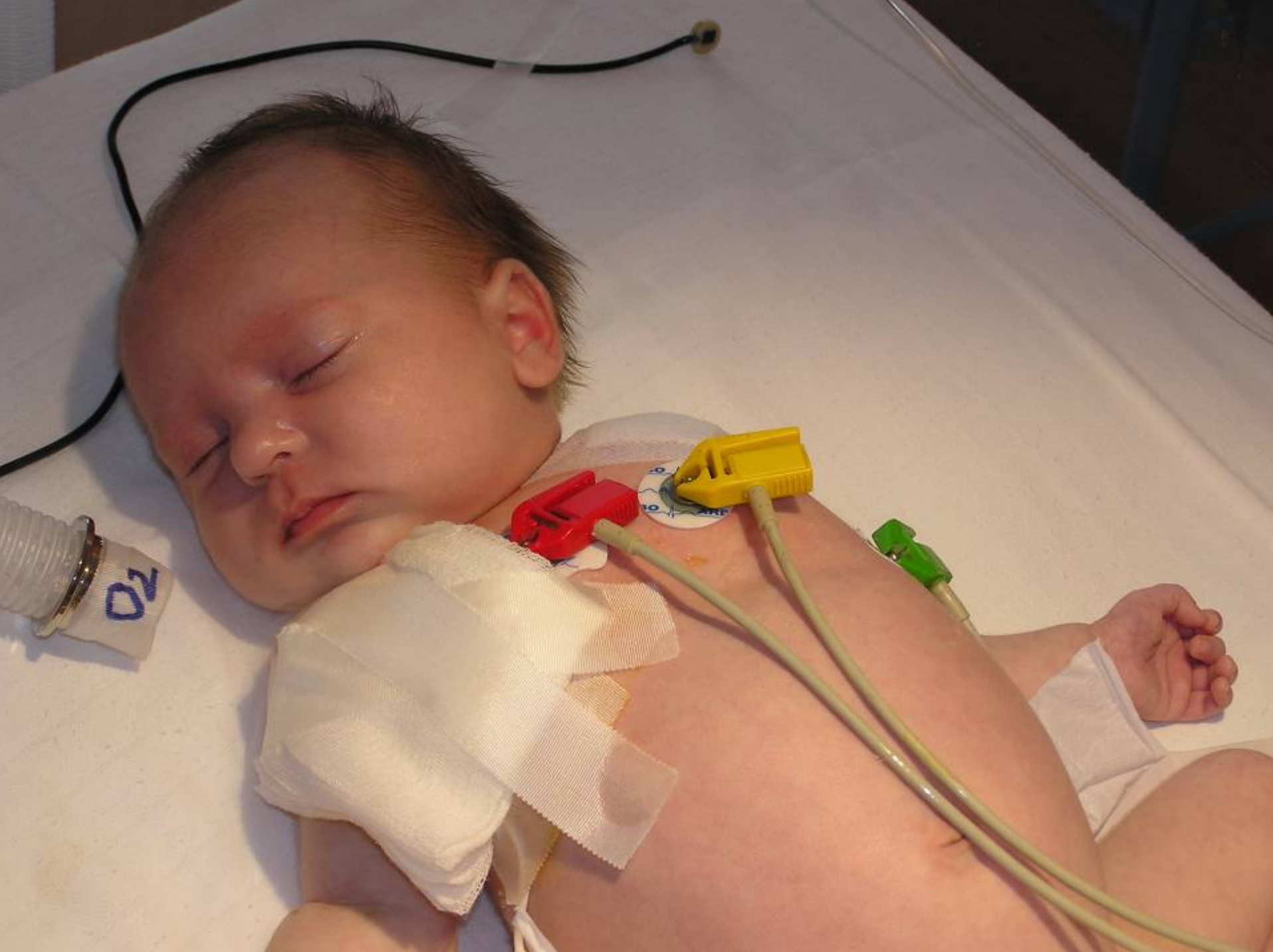
- 29th day of life

- fever
- hepatomegaly (+5cm), splenomegaly (+5cm)
- WBC 14x10^9/l, Hb 97g/l, Plt 55..33x10^9/l
- coagulopathy

- admission to pediatric department, therapy with ATB

- bone marrow aspiration – susp. ALL

- 30th day of life - transfer to our hospital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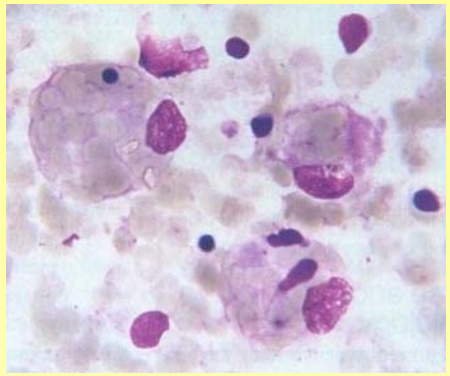
Clinical, laboratory and histopathological findings



- hepatosplenomegaly
- fever

- cytopenia - anemia, trombocytopenia (.. $16x10^9/l$)

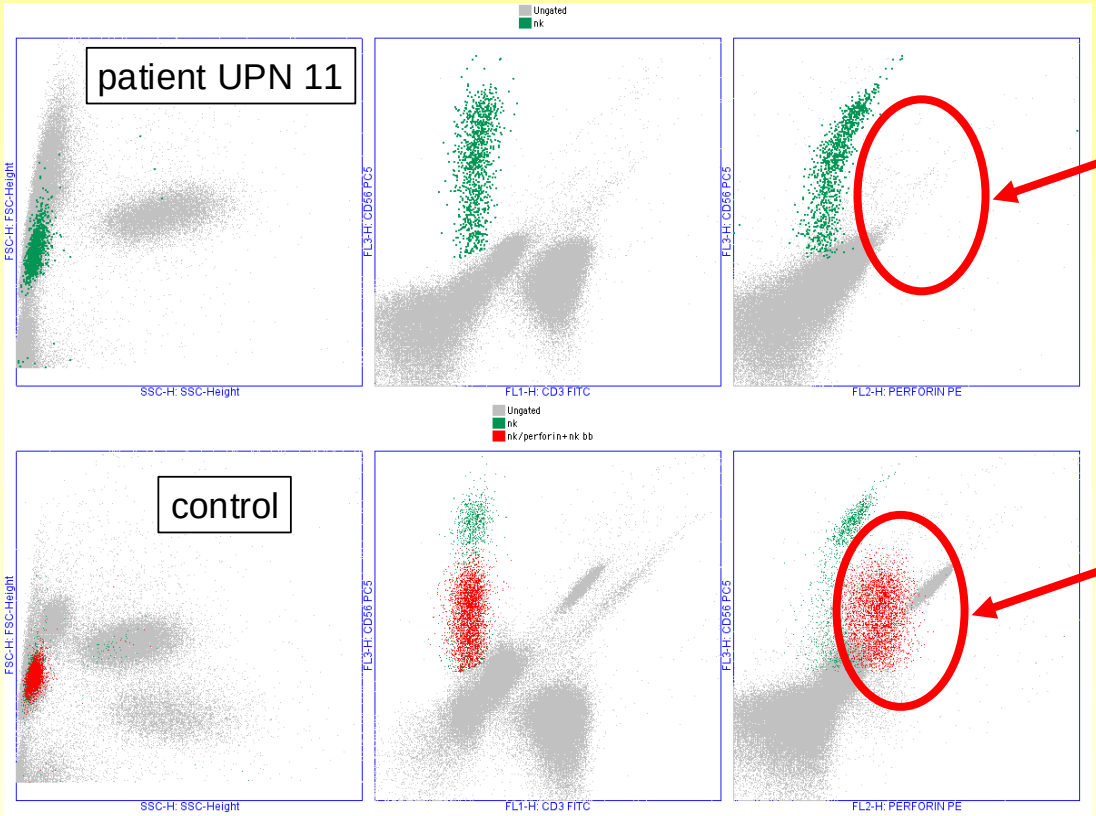
- ⬆ triglycerides (3,29 mmol/l)
- ⬇ fibrinogen (0,89 g/l)
- ⬆⬆ ferritin (7816 .. 40640 µg/l)

- hemophagocytosis in bone marrow aspiration

- no CNS involvement

Perforin expression - FC

Flow cytometric analysis. Dot plot.



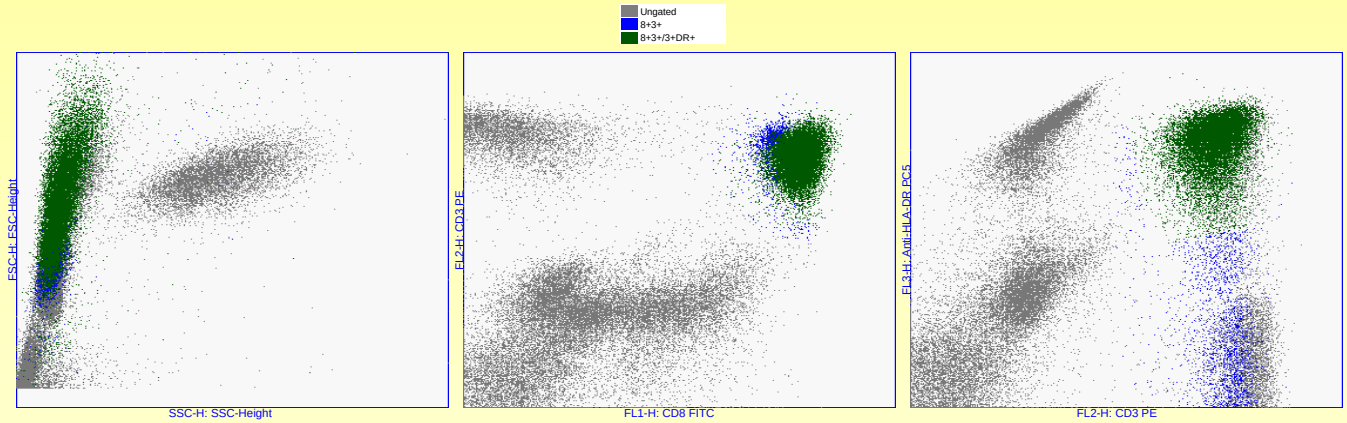
perforin deficiency

normal perforin expression in control patient

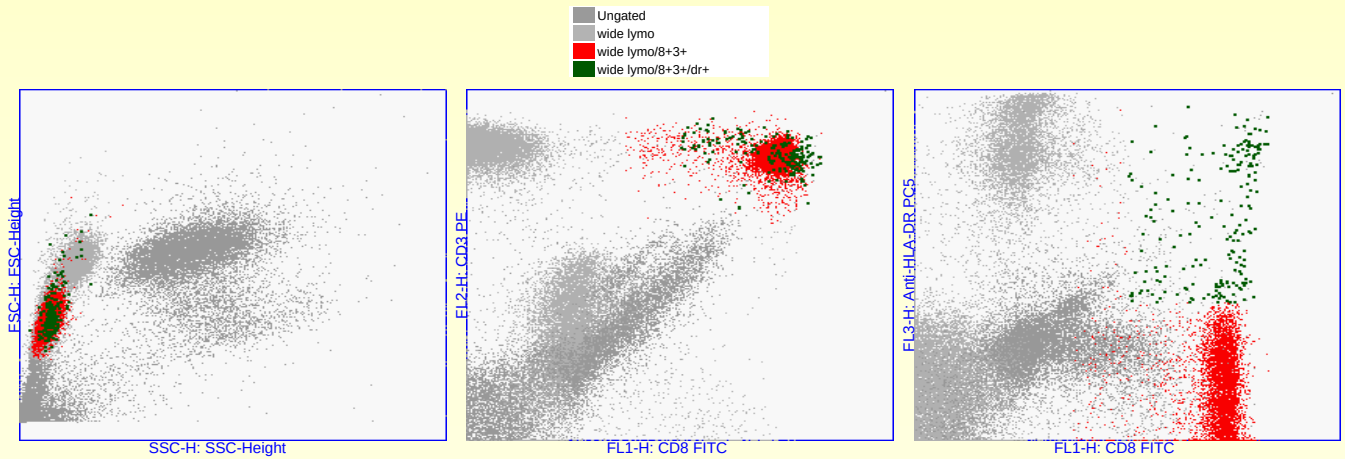
HLA DR expression

HLA DR expression on CD8+3+ T cells at
A diagnosis in peripheral blood (88%) and
B after HLH 2004 treatment in remission prior to BMT

A

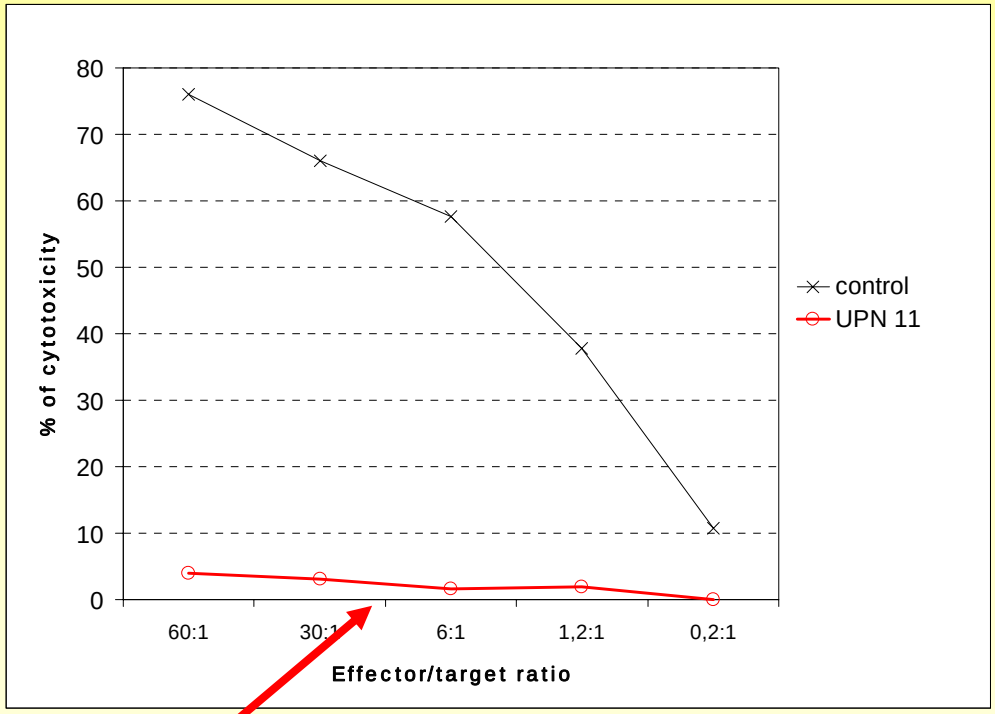


B



Cytotoxic assay

Cytotoxic activity of T-lymphoblasts generated from T-cells
Target cells: L1210 cells deficient in FAS expression



Defective cytotoxic activity of patient's lymphoblasts

Therapy – HLH 2004

- 4.8.2004 ..... day of admission

- 5.8.2004 VP-16, dexamethasone, cyclosporine A
- non identical sibling ➔ MUD search initiated

- 5.8. sepsis (Acinetobacter)
- 6.8. progression of hepatosplenomegaly
  respiratory insufficiency
- 6.8.-11.8. arteficial ventilatory support

- 18.8. sepsis (Pseud. aeruginosa, Staph. haemolyticus)

- 8.10. admission to BMT unit for unrelated SCT

Stem cell transplantation

- 19.10.2004 (aged 3,5 months)
- donor: MUD, 9/10 (Cw), PBSC (CD34+ $8x10^6$/kg)

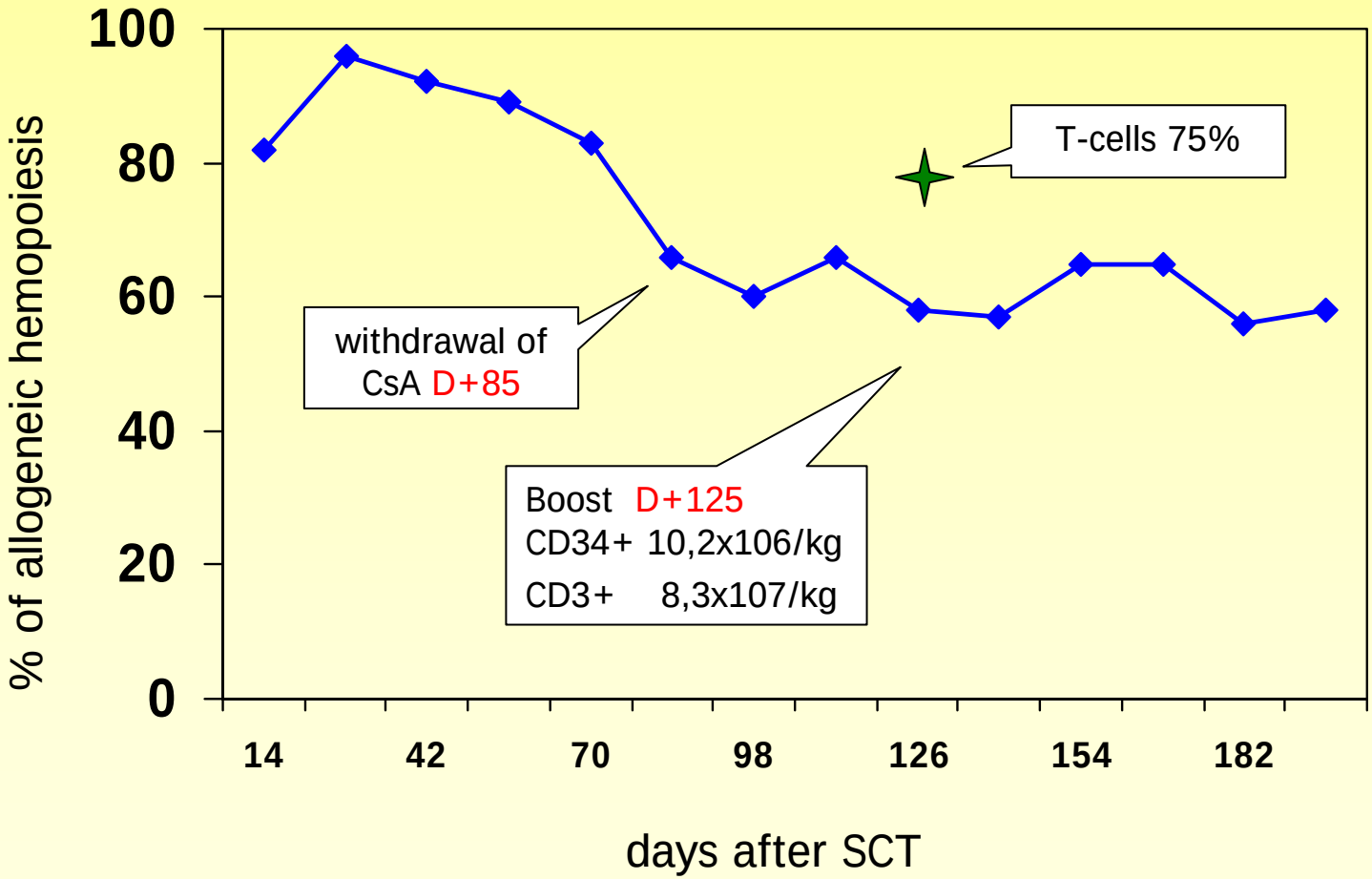
- conditioning: Busulfan, VP-16, Cyclophosphamide, ATG
- GVHD prophylaxis: Cyclosporine A, Methotrexate

- engraftment: ANC D+15, Plt D+19
- GVHD: none

- complications: febrile neutropenia D+2, nefropathy

- discharge from BMT unit: D+85 (aged 6 months)

Hemopoietic chimerism



D+180 after SCT

- no GVHD, no signs of FHL reactivation
- stable MC in peripheral blood and MC in T-lymphocytes (75% of allogeneic hemopoiesis)

➔ might be curative for FHL

Thank you

for attention