Treatment of a Patient with Complete diGeorge/CHARGE Syndrome

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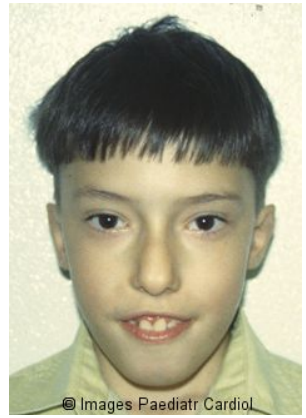
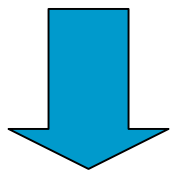
Syndrome DiGeorge



- 1967 – Dr Angelo diGeorge
- defined by phenotype
- DGS triad
  - **congenital heart defects**
  - **immune deficiency** secondary to a/hypo/plasia of thymus
  - **hypocalcaemia** due to small or absent parathyroid glands
- initially considered rare
- current estimate: **1 in 4,000** live births
- monoallelic microdeletion 22q11.2 (90% of cases)
- the most common microdeletion syndrome in humans

Nomenclature

- **DGS** DiGeorge Syndrome
- **VCFS** VeloCardioFacial Syndrome (Shprintzen)
- **CTAFS** ConoTruncal Anomaly Face Syndrome (Takao)



same entity because of **del22q11**

„CATCH 22“ or „22q11 deletion syndrome“?

CATCH 22

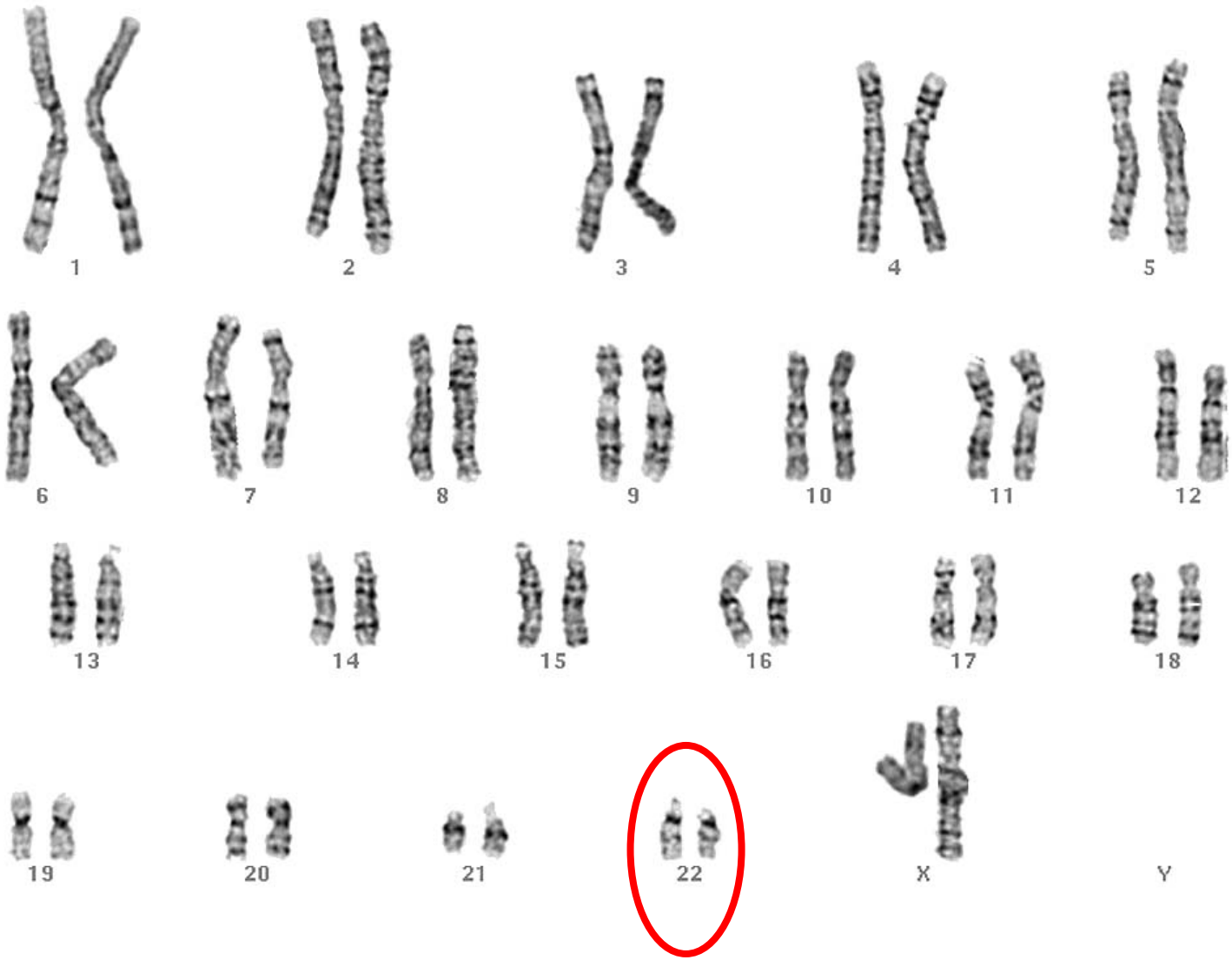
- *Cardiac defects, Abnormal face, Thymic hypo/aplasia, Cleft palate, Hypocalcemia, deletion 22q11*
- negative connotations (Joseph Heller’s book)

→ pessimism, self-dispair

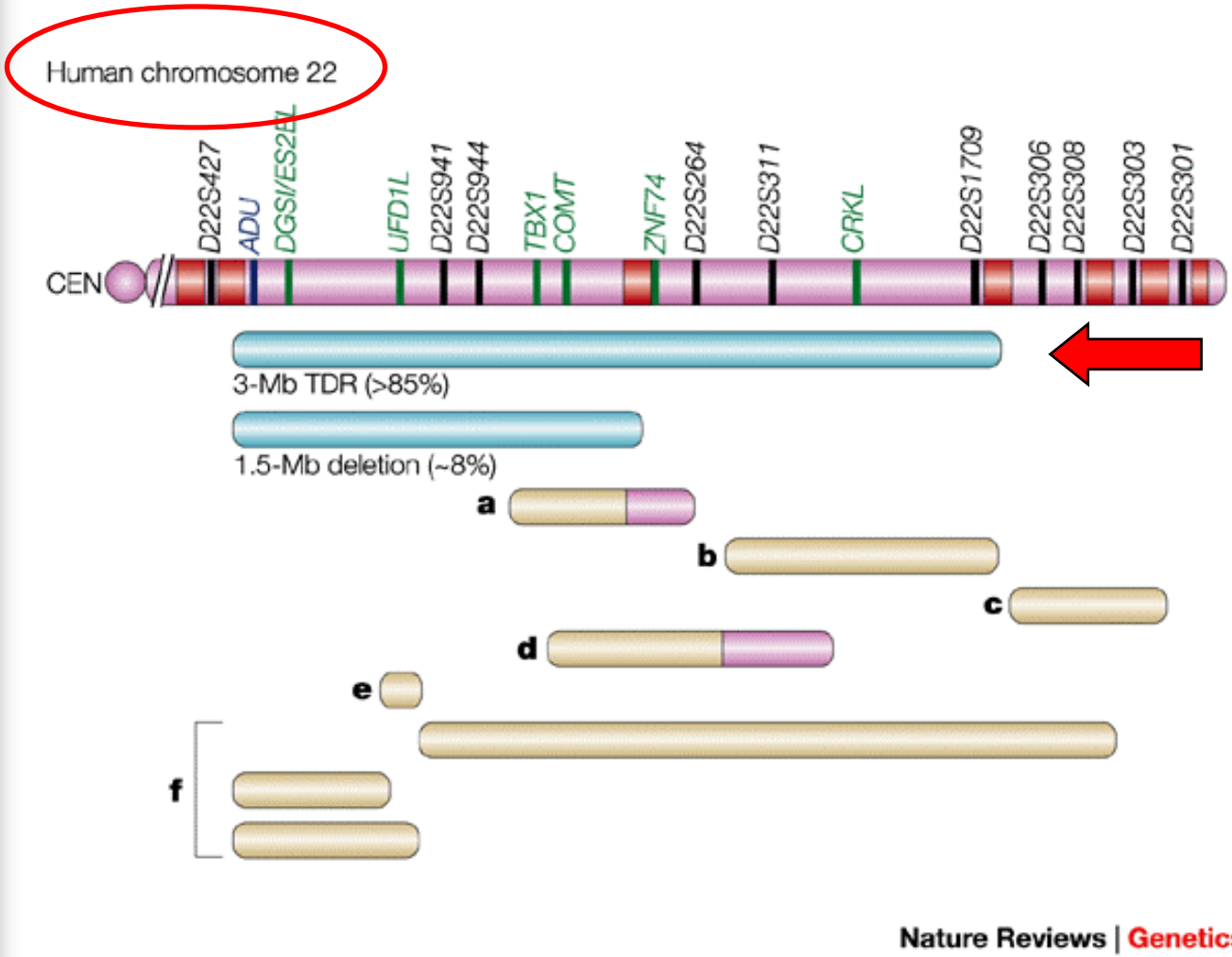
22q11 deletion syndrome

- probably better for description of this condition

DiGeorge syndrome



22q11 region



The common 3 Mb typically deleted region (85% of *del22q11* patients)

the 1.5-Mb deletion (8% of patients)

a–f Individual patients with unusual deletions

Lindsay, Nature Reviews Genetics 2; 858-868 (2001)

DGS without 22q11.2 deletion

- only **10%** of pts with DGS lack 22q11.2 deletion
- **environmental factors** (foetal exposure):
  - alcohol
  - retinoic acid
  - maternal diabetes
- **other genetic factors**:
  - del10p13
  - del17p13

Complete DiGeorge Syndrome (cDGS)

- in 1-5 % patients with DGS
- severe immunodeficiency
- aplasia of thymus
- no or very low number of T cells
- fatal if left untreated
- <50% patients have del22q11.2

CHARGE Syndrome

Coloboma
Heart defects
Atresia choanae
Retarded growth
Genital anomalies
Ear anomalies

CHARGE

Chromodomain **H**elicase **D**NA-binding

- the origin of CHARGE remains indefinite, however, **CHD7 gene** at locus 8q12 is currently being investigated as a candidate gene
- the chief phenotypical features of CHARGE distinguishing it from DGS are **coloboma** and **choanal atresia** as these are uncommon findings in DGS or 22q11.2 deletion phenotypes

CHARGE + cDGS

- overlapping phenotype?
- stand-alone entity?
- usually **no 22q11.2 deletion**

Possible therapeutical approaches in patients with cDGS

- thymus transplantation
- bone marrow transplantation (BMT)
- peripheral blood monocyte cells transplantation (PBMCT)

X

palliative approach

ethical dilemma?

Transplantation of thymus

- **post-natal** thymus tissue (from infants younger than 6 months)
- no **HLA match**, however, pts with closest HLA matching developed the T cells more rapidly
- all pts developed T-cell proliferative responses to mitogens
- pts have many infections in the first 100 days after the transplantation
- 12 pts, **58% survival** with 15 months to 8.5 years of follow-up
- good result in **comparison with SCID** treated with BMT (survival 75-80%), these pts with no major congenital abnormalies (e.g. heart defect, etc.)
- not available in Europe?

- 5 pts with **CHARGE** transplanted, 3 pts died

  (intracerebral hemorrhage, hemorrhage during abdominal surgery, sepsis)

Markert, M. L. et al. Thymus transplantation in complete DiGeorge syndrome: immunologic and safety evaluations in 12 patients. Blood 102, 1121-30 (2003).

Bone Marrow Transplantation

- 7 months, female, **$1.2x10^9$/kg** of from brother (DR mismatch)
- no conditioning, no GVHD profylaxis

- T cell engraftment, CD4>400 cells/uL after 12 months
- PHA normal - in couple of months, normal response to vaccination
- clinically ok, developmental delay, several episodes of otitis media, Shigella gastroenteritis
- **well after 3 years post-BMT**

Goldsobel, A.: Bone marrow transplantation in DiGeorge syndrome. J Pediatr 111, 40-44 (1987)

BMT 2

- 5 months, female, **$4.3x10^8$cells/kg** from HLA-identical brother
- no conditioning, no GVHD prophylaxis

- T cell engraftment, CD4>400 cells/uL after 1 month
- PHA normal after 8 months
- **well after 2 years post-BMT**

Borzy, M.: Successful bone marrow transaplantation with split lymphoid chimerism in DiGeorge syndrome. J Clin Immunol 9, 386-392 (1989)

BMT 3

- 13 months, **$8.0x10^8$ cells/kg**, HLA-identical sibling, rATG – insuficient no engraftment
- 19 months, busulfan, cyclophosphamide, CyA+MTX – GVHD prophylaxis

- chimerism (D+18), complete engraftment (D+28), CD4>400 cells/uL after 1 month
- engraftment of mononuclear cells and granulocytes (different from previous cases)
- PHA normal after **10 months**
- naive (CD4+45RA+) significantly increased → did the patient have a thymus?

Matsumoto, T. et al. Complete-type DiGeorge syndrome treated by bone marrow transplantation. Bone Marrow Transplant 22, 927-30 (1998).

BMT 4

- 1st patient
  - 1 haploidentical BMT (**T-cell depleted**) ➡ died
- 2nd patient
  - 3 haplo-identical BMT (**T-cell depleted**)
    - no conditioning, no engraftment
  - 4th BMT together with thymic tx ➡ died

Markert, M. L. et al. Complete DiGeorge syndrome: persistence of profound immunodeficiency. J Pediatr 132, 15-21 (1998)

Why should BMT work in cDGS?

- induction of **thymic** differentiation by T cells (?)
  - activation of hypoplastic thymus
  - thymus could be present even if undetected by MRI
  - recent thymic emigrants, thymic hormones
- expansion of **extrathymic** T cells (?)
  - increment in gamma/delta T cells
  - Vβ repertoire on CD4+ and CD8+ cells
- **post-thymic precursor cells**
  - able to expand in peripheral lymph nodes without contact with thymus, or long-lived T cells were infused from donor, and these cells increase by various means

Peripheral Blood Monocyte Cells Transplantation

- 4 years (!), male, HLA-identical sister, **24x10^6 cells/kg**
- no conditioning, GVHD prophylaxis – CyA+mycophenolate mofetil

- mixed chimerism only in T-cell population, exclusive memory phenotype , absence of TRECs, B and NK cells exclusively of recipient origin
- PHA normal, specific Ab produced after immunization
- anti-thyroglobulin autoantibodies disappeared (!?)
- **well after 6 years**, stable level of CD3+ cells
- T cell proliferations to mitogen are still normal

Bensoussan, D. et al. T-cell immune constitution after peripheral blood mononuclear cell transplantation in complete DiGeorge syndrome. Br J Haematol 117, 899-906 (2002)

PBMCT 2

- 2 months, male, HLA matched brother, 10ml of peripheral blood without mobilisation**, $4x10^6$ CD3+ cells/kg**
- no conditioning, no GVHD prophylaxis
- 2nd transplant at 7 months, **$2x10^7$ CD3+ cells/kg**

- T-cell counts, PHA normal after 1 week, no GVHD
- good response to immunization
- CD3+ – plateau at 315 cells/uL **after 75 weeks**
- no oportunistic infection
- approx. 50% chimerism

Bowers, D.:A. Immune constitution of complete DiGeorge anomaly by transplantation of unmobilized blood monunclera cells. Lancet 352, 1983-84 (1998)

Case report

Perinatal history

- Caucasian male
- born on June 18th, 2004
- healthy parents, no consanguinity, no siblings
- 1st pregnancy
- polyhydramnion → amniocentesis → normal karyotype 46,XY
- term delivery, foetal hypoxia → Caesarean section → resuscitation, intubation, artificial ventilation

Symptoms

- hypertelorism (wide-set eyes)
- malformed low-set ears
- micrognatia (small chin)
- bilateral choanal atresia
- esophageal atresia with tracheobronchial fistula
- congenital heart defects (haemodynamically significant ductus arteriosus, right-sided aortal arch and foramen ovale apertum)
- bilateral retinal coloboma
- tracheobronchomalacia $\rightarrow$ apnoic pauses
- severe gastroesofageal reflux
- retention of testis and micropenis
- recurrent infections, septicaemia
- recurrent respiratory distress $\rightarrow$ artificial ventilation
- absence of T cells – 21 cells/μL, no response to mitogens (2 mos)
- absence of thymus (MRI, surgery)

DiGeorge syndrome?

- **low T-cells?**
  - *yes*
- **absent thymus?**
  - *yes*
- **hypocalcemia?**
  - *yes (however no seizures)*
- **heart defect?**
  - *yes*
- **microdeletion at 22q11.2?**
  - *no (no other genetic tests done)*

CHARGE Syndrome

Coloboma	*yes*
Heart defects	*yes*
Atresia choanae	*yes*
Retarded growth	*yes*
Genital anomalies	*yes*
Ear anomalies	*yes*

Surgical interventions

- esophageal atresia + TE fistula
- bilateral choanal atresia
- congenital heart defects
- fundoplication – insertion of gastric tube

1st BMT

- at 6 months (4 months after diagnosis)
- unrelated donor from Canada, 8/10 (B, CW)
- no conditioning, no GVHD prophylaxis
- **1x10^6/kg CD3+;** 0.2x 10^6/kg CD34+ (bone marrow)
- non-irradiated blood products administered
  (7 times prior 1st BMT, 1 time after 1st BMT)

Chimerism VNTR (D+10)

- donor detected
- no other signal detected (transfusions)

Complications (D+10)

- skin aGVHD(stage 3, grade II)
- sepsis, cardiopulmonary instability. capillary leakage sy, ileus

2nd BMT

- at 7 months, D+36 after 1st BMT
- **0.89x 10^6/kg CD3+,** the same donor, no conditioning
- prevention of GVHD: CsA

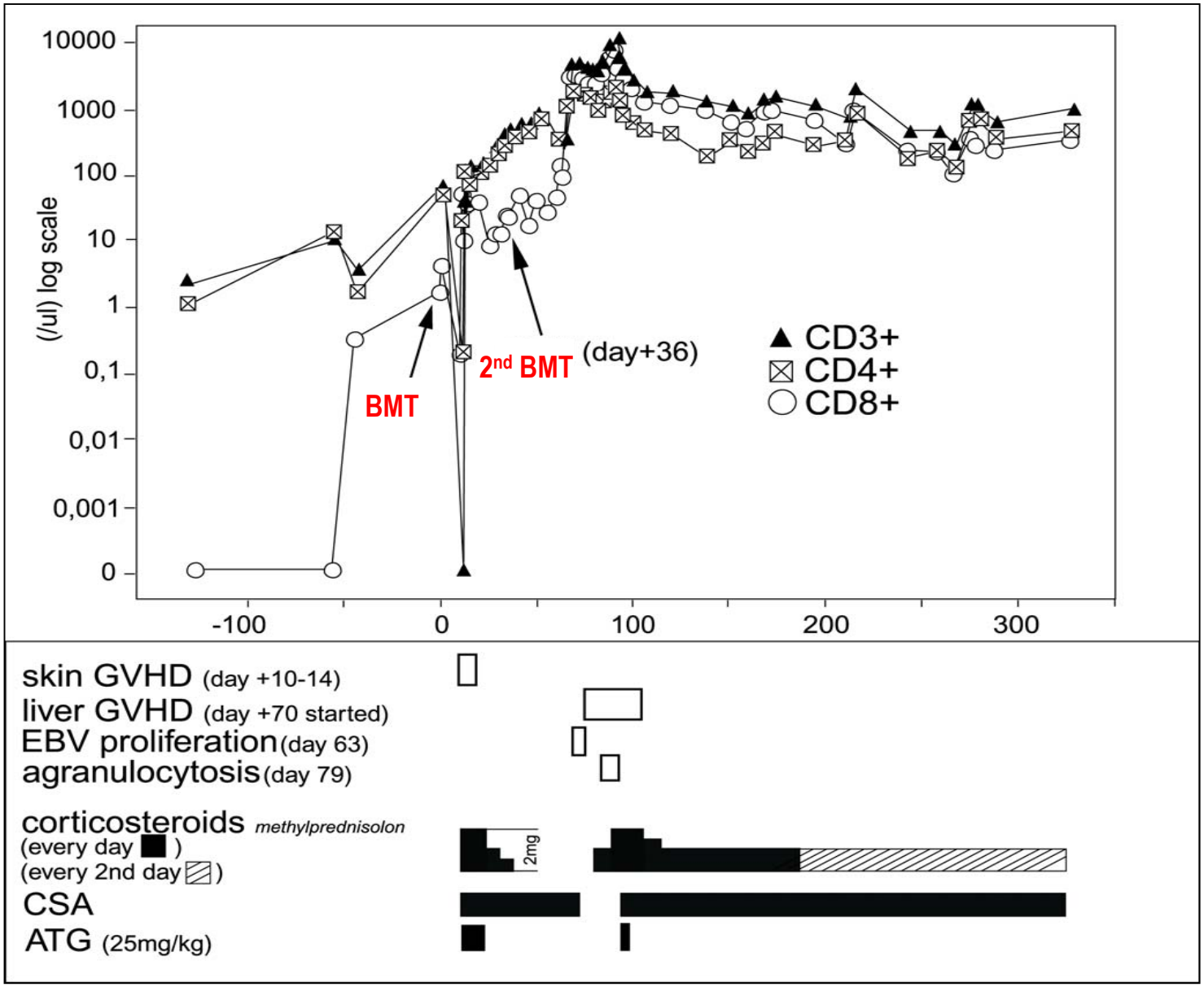
EBV infection D+27

- B cell proliferation
- oligoclonality
- no clinical manifestation
- withdrawal of CsA
- rituximab (375 mg/m^2)
- proliferation of CD8+ activated T cells started

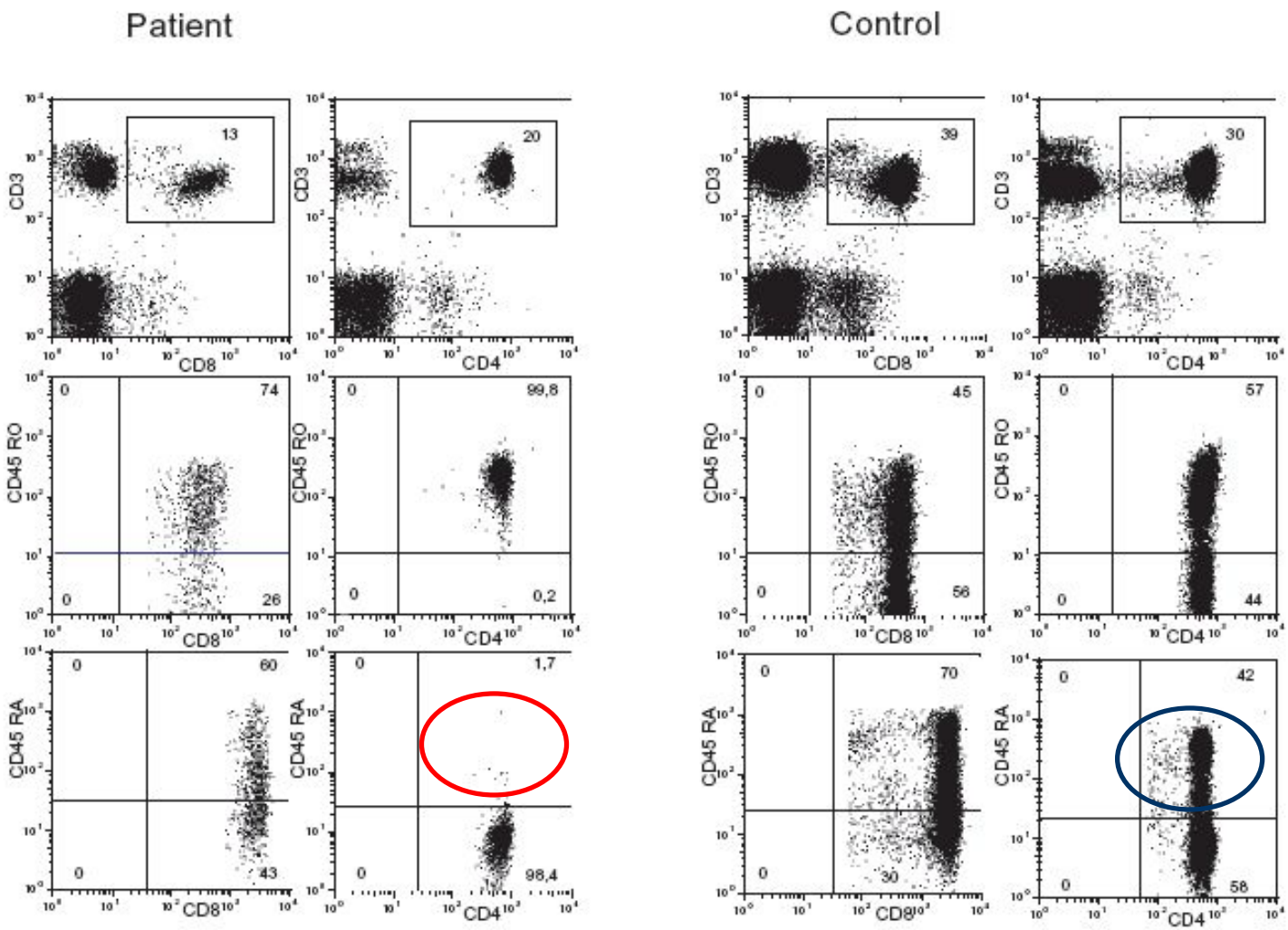
Complications

- liver GVHD
- agranulocytosis

T cells on Log scale



Memory versus Naive T cells



Current status

- D+517 after 1st DLI, age 22 months
- out-patient mode
- no infections
- normal liver function
- slight gradual psychomotorical development
- apnoic pauses – now rarely
- immunosuppression – stopped
- IVIG – stopped
- problem with feeding (via gastric tube)

Problems patient may face in the future

- **exhaustion of the graft, apoptosis**
  - increased susceptibility of CD4+ cells to apoptosis following stimulation (regulatory effect
  - loss of part of relevant T-cell repertoire

- **autoimmunity**
  - due to exclusive peripheral expansion of T cells without thymic selection
  - continuous thymic output ensures that self-reactive T-cells are maintained at a very low frequencies in the periphery

- problems caused by **other abnormalities**

Conclusion

- **low dose BMT** from unrelated donor in patients with DGS is a functional treatment alternative option

- care for the patients with complete DGS is very difficult as they suffer from **various serious medical problems** and poor immunological status is only one of them

our patient...

...and his former home

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