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Saving the red baby: Successful allogeneic cord blood transplantation in Omenn syndrome

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Abstract Haematopoietic stem cell transplantation is the treatment of choice for severe primary immunodeficiencies, but only has moderate prognosis in Omenn syndrome as it is complicated by highly activated Omenn T-cells resulting in delayed T-cell engraftment and a high rate of graft failure. A 6 1/2 months old patient with a previously unknown compound heterozygous defect within the *RAG1* gene (R474C; R975W) underwent 8/10 HLA-matched cord blood transplantation after myeloablative conditioning. Immune reconstitution was impressive with T-, B- and NK-cells reaching the median of age-dependent reference values within twelve, four and two months respectively. With a continuous decrease of activated Omenn T-cells there was a steady increase of naive, probably thymus-derived T-cells. Polyclonal B-cell activation and hypergammaglobulinaemia disappeared with B-cell engraftment. This case emphasizes that, despite their naive status and HLA-barriers, cord blood T-cells were apparently able to achieve T-effector function resulting in the elimination of all activated Omenn T-cells.

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Introduction

Neonatal and infantile erythrodermas represent heterogeneous conditions ranging from self-limiting diseases with excellent prognosis to severe illnesses with significant morbidity and mortality. If early-onset erythroderma is accompanied by systemic symptoms, particularly severe infections and failure to thrive, a rapid diagnosis and effective multidisciplinary treatment is pivotal for immediate survival and future outcome, especially in a subset of

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infants suffering from severe combined immunodeficiency (SCID) and the Omenn syndrome (OS, OMIM # 603554) [1,2].

OS represents a genetically heterogeneous, autosomal recessive primary immunodeficiency (PID) characterized by lymphadenopathy, hepatosplenomegaly, exfoliative erythroderma, massively increased IgE and eosinophilia. Differential diagnosis includes the Wiskott-Aldrich syndrome (WAS) characterized by x-linked inheritance and thrombocytopenia [3], the Netherton syndrome (NS) with abnormal epidermal LEKTI expression [4] and the Hyper-IgE syndrome (HIES), which is associated with mutations in the transducer and activator of transcription 3 gene (*STAT3*) [5]. OS is predominantly caused by mutations in the recombination activating genes 1 and 2 (*RAG1/RAG2*) [6,7] or the nonhomologous end-joining factor *Artemis* [8], which interfere with somatic diversification of T- and B-cell receptor-encoding genes. Furthermore, mutations of the Interleukin-7R α chain [9] result in disturbed proliferation of early thymocyte progenitors. All that leads to oligoclonal expansion of autoreactive T-cells and a marked reduction of circulating B-cells ("T⁺B⁻SCID") [6].

Both SCID and non-SCID immunodeficiencies are treatable by haematopoietic stem cell transplantation (HSCT). In the recent decade cord blood (CB) has been used successfully as an alternate stem cell source for HSCT [10]. However, it is unclear whether CB is also a feasible option in OS, in which the outcome after HSCT is somewhat poorer than in conventional SCID. Here we report on successful HLA-mismatched cord blood transplantation (CBT) after myeloa-

blative conditioning in a patient with OS presenting as infantile erythroderma.

Methods and results

A 3-month-old girl, born as first child to non-consanguineous parents, suffered from exfoliative erythroderma, persistent pruritus, alopecia, food intolerance and failure to thrive. Beside prominent splenomegaly and generalized lymphadenopathy, clinical examination revealed ichthyosiform erythroderma with marked pachydermia, onychodystrophy and alopecia while eyebrows and eyelashes appeared normal. The infant's general condition stabilized rapidly under parenteral fluid substitution, broad spectrum antibiotics, enteral feeding with highly hydrolyzed cow's milk formula and baseline emollient therapy consisting of panthenol ointment and daily oil baths. Beside hyponatremia (152 mmol/l), hypoprotei-nemia (2.8 mg/dl), C-reactive protein elevation (3.0 mg/dl) and anemia (8.0 g/dl), a massively elevated total serum IgE level and white blood cell count (WBC) with 39% eosinophils and 30% lymphocytes were detected (see Table 1). Lymphocyte phenotyping by flow cytometry (FACS) showed a strongly decreased B-cell fraction (CD20⁺) while T-cells consisted mainly of highly activated memory T-cells (CD3/DR⁺, CD4/45RO⁺; see Fig. 1 and Table 1). Chimeric T-cells of maternal origin were not detected [11].

As the findings had become highly suspicious for OS, an immunosuppressive therapy with systemic ciclosporine A

Table 1 Results of pre- and posttransplant white blood cell count, immunoglobulin levels and lymphocyte phenotyping by flow cytometry (FACS)

Parameter	Before CBT		3 months after CBT		12 months after CBT	
White blood cell count	53.000/ μ l		7.500/ μ l		9.400/ μ l	
Eosinophils	20.670/ μ l	39%	1.200/ μ l	16%	376/ μ l	4%
Lymphocytes	16.006/ μ l (3.700–9.600/ μ l)	30%	1.275/ μ l (2.600–10.400/ μ l)	17%	5.640/ μ l (2.700–11.900/ μ l)	60%
Immunoglobulin G (IgG)	815 mg/dl		715 mg/dl		573 mg/dl	
Immunoglobulin A (IgA)	410 mg/dl		29 mg/dl		n.d.	
Immunoglobulin M (IgM)	303 mg/dl		218 mg/dl		82 mg/dl	
Immunoglobulin E (IgE)	7.120 IU/dl		349 IU/dl		n.d.	
CD4/CD3	3.841/ μ l (1.500–5.000/ μ l)	24%	634/ μ l (1.000–4.600/ μ l)	50%	2.999/ μ l (900–5.500/ μ l)	53%
CD8/CD3	11.204/ μ l (500–1.600/ μ l)	70%	89/ μ l (400–2.100/ μ l)	7%	1.302/ μ l (400–2.300/ μ l)	23%
CD3/DR	10.564/ μ l (70–500/ μ l)	66%	139/ μ l (100–600/ μ l)	11%	91/ μ l (100–700/ μ l)	2%
CD4/45RO	3.841/ μ l	100%	621/ μ l	98%	690/ μ l	23%
CD4/45RA	0/ μ l	0%	38/ μ l	6%	2.279/ μ l	76%
45RO/CD8	11.204/ μ l	100%	69/ μ l	78%	117/ μ l	9%
45RA/CD8	112/ μ l	1%	22/ μ l	25%	1184/ μ l	91%
CD20	31/ μ l	1%	38/ μ l	6%	330/ μ l	11%
CD3/CD56	38/ μ l (100–1.300/ μ l)	1%	171/ μ l (200–1.200/ μ l)	27%	270/ μ l (100–1.400/ μ l)	9%
CD3/CD25	3.188/ μ l	83%	272/ μ l	43%	450/ μ l	15%
CD4/CD25	n.d.		247/ μ l	39%	210/ μ l	7%

Age-matched reference values (5th to 95th percentiles) are shown in parentheses [14]; n.d. not done.

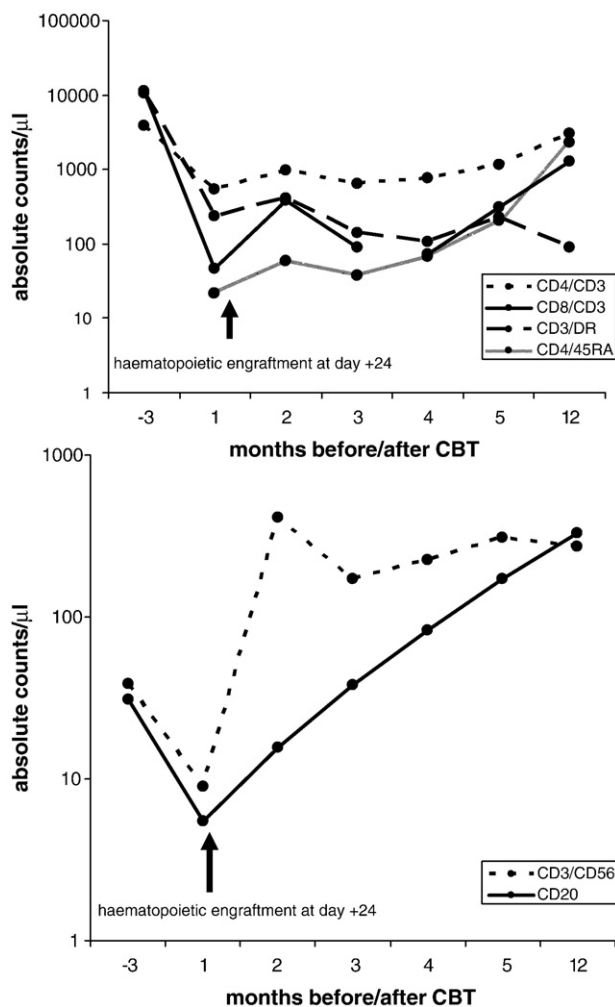


Figure 1 Results of pre- and posttransplant lymphocyte phenotyping by flow cytometry (FACS). Absolute cell counts of CD4, CD8, HLA-DR, CD45RA, CD56 and CD20 are presented on the y-axis. The x-axis shows the different time points to haematopoietic stem cell transplantation.

(CSA, 2×4 mg kg^{-1} daily) and topical tacrolimus ointment twice daily was initiated leading to reduction of WBC and clear amelioration of skin symptoms. Molecular analysis of peripheral blood mononuclear cells (K. Schwarz, Institute for Clinical Transfusion Medicine and Immunogenetics, Department of Transfusion Medicine, University Hospital Ulm, Germany) revealed a compound heterozygous defect within the *RAG1* gene (R474C; R975W). Since no matched sibling or unrelated donor was available the child received an 8/10 HLA-matched (DRB1- and DQB1-mismatch) CB consisting of 1.8×10^8 total nucleated cells/ kg^{-1} at the age of 6 1/2 months. Myeloablative conditioning included busulfane (days -11 to -8; 4 mg kg^{-1} daily), fludarabine (days -7 to -4; 40 mg kg^{-1} /30 [adjusted to body weight] daily), cyclophosphamide (days -3 to -2; 50 mg kg^{-1} daily) and rabbit anti-thymocyte globulin (ATG, Fresenius Biotech GmbH, Graefelfing, Germany) on days -14 to -12 and -4 to -2 (20 mg kg^{-1} daily) for elimination of activated T-cells. Acute Graft-versus-host Disease (GvHD) was graded according to previously described criteria [12] and prevented by CSA on days -1 to +20 and by FK506 thereafter due to

arterial hypertension and reduced CSA-uptake. On day +6 WBC rose to $3800 \times 10^9/\mu\text{l}$ with detection of highly activated T-cells and prodromal erythroderma. The nature of this T-cell proliferation remained unclear as HLA-typing of these activated T-cells was not performed, but they were antagonized successfully by one additional dose of ATG (20 mg kg^{-1}). Engraftment ($>1.0 \times 10^9/\mu\text{l}$ leukocytes and $>0.5 \times 10^9/\mu\text{l}$ neutrophil granulocytes for three consecutive days) was reached at day +24 followed by acute GvHD III° of the liver and intestine which was treated effectively with cortisone (2 mg kg^{-1} daily). While recurrent bacterial infections were treated readily with broad spectrum antibiotics, no fungal or viral infections occurred. Successive chimerism analyses [13] revealed complete engraftment on day +33 while erythroderma and associated pruritus regressed rapidly. Further immunological investigations did not detect the recurrence of autologous lymphocytes even after complete discontinuation of post-transplant immunosuppressive therapy at the age of one year. Within 12 months CD4 counts reached the median of age-dependent reference values [14] (see Fig. 1 and Table 1). There was a continuous decrease of activated T-cells (CD3+/HLADR+) which was paralleled by a slow but steady increase of naive probably thymus-derived CD4 and CD8 cells. B-cell engraftment was fast within four months resulting in a disappearance of polyclonal activation and hypergammaglobulinaemia. Interestingly, NK cells showed an expansion on week two and reached the age-dependent reference values already by the age of two months. At the last follow-up 1 1/2 years after HSCT the patient was in good general condition.

Discussion

The diagnostic workup of neonatal erythroderma is facilitated by only a few laboratory tests including a full WBC, determination of serum immunoglobulins (IgG, IgA, IgM, IgE) and lymphocyte phenotyping by FACS. As demonstrated in our infant, erythroderma, massively elevated IgE and T-cell lymphocytosis is highly indicative of OS [1]. Interestingly, we find high values of serum immunoglobulins despite the subtotal lack of B-cells in peripheral blood. This may be explained by residual B-cell differentiation to plasma cells in lymphoid tissues. Diagnosis was confirmed by identifying the patient to be compound heterozygote for two so far unpublished mutations in the *RAG1* gene. Both mutations are missense mutations possibly enabling a partial activity of the *RAG1* mutants [6,7].

Due to potentially fatal sequelae, management of infants with SCID has to be considered a paediatric emergency. The acute treatment of erythrodermic neonates and infants has to be initiated on a symptom-oriented basis with a particular emphasis on infections, hypertonic dehydration, hypoproteinemia and hypothermia caused by a massively impaired skin barrier function [15]. In this context, it is pivotal to aggressively treat infections and to stabilize epidermal homeostasis by incubator care ensuring an environment with a high humidity level. Additionally, feeding with a highly hydrolyzed cow's milk formula is warranted and immunosuppressive therapy with ciclosporin A +/- systemic corticosteroids is necessary to alleviate symptoms caused by extremely activated autoreactive T-cells [16].

Nevertheless, curative therapy can only be achieved by HSCT. With the further development of HLA-matching, antibacterial, antiviral and immunosuppressive therapy the overall survival of OS patients, even after mismatched and unrelated HSCT, strongly improved [17,18]. Thus, in a predominately haploidentical transplanted cohort an overall survival of 81.8% was reported [19] whereas 87.5% of recipients of mismatched related and matched unrelated bone marrow survived [20]. But autologous reconstitution of highly activated and aggressive Omenn T-cells still poses a challenge, even in haploidentical T-cell depleted HSCT (haploHSCT) [1].

Furthermore, unrelated HLA-matched HSCT may be complicated by the time-consuming search for a suitable donor. In contrast, access to CB is fast and the cell dose is generally adequate for performing CBT in the first year of clinical presentation [10]. Another advantage of CB is the immunological naivety of CB-derived T-cells resulting in a lower GvH risk and therefore enhanced immune reconstitution [21,22]. Beside the low rate of viral contamination in cryopreserved CB cells, the ability to infuse T-cells with the graft constitutes another advantage resulting in earlier immune recovery and potential elimination of pre-existing infections. As a consequence, rapid reconstitution of B- and antigen-specific T-cells is described after CBT [22–24] whereas T- and B-cell recovery is delayed in haploHSCT [25,26]. Disadvantageous is the lack of availability of the donor for a boost HSCT and the lack of viral specific cytotoxic T-cells in CB which may favour opportunistic infections [27].

After the first description of successful CBT after myeloablative conditioning in OS in 1999 [28], only a few more cases have been reported. Recently, a detailed review on CBT in PID reported an overall survival of 67% (2/3 pts) in 6/6 and of 100% (4/4 pts) in 5/6 HLA-matched CBT [27]. Furthermore, CBT was performed successfully in a patient with Omenn-like syndrome, characterized by detection of maternal lymphocytes resulting in a GvHD-like picture [29]. Although CBT in OS was also favourable after reduced intensity conditioning [30,31], it is most frequently preceded by a myeloablative and immunosuppressive conditioning regimen to ensure enough haematopoietic space for trilineage engraftment and to prevent graft rejection induced by highly activated autologous Omenn T-cells [26]. Accordingly, our conditioning regimen consisted of both myeloablative and immunosuppressive parts resulting in tolerable and readily treatable adverse effects. Despite lack of viral specific cytotoxic T-cells in the graft and the use of ATG we did not observe any viral infections. Therefore, this conditioning regimen may act as a reference for future HLA-mismatched CBT in OS.

In our case there was an impressive immune reconstitution after CBT with T-, B- and NK-cells reaching the median of age-dependent reference values within twelve, four and two months respectively [14]. Despite their naivety, CB T-cells were apparently able to achieve a T-effector function that resulted in the elimination of all highly activated autologous Omenn T-cells. In addition, the use of ATG and the expansion of NK cells may have played a role in the elimination of Omenn T-cells.

In conclusion, this case emphasizes that infantile erythroderma represents a potentially life-threatening condition that has to be treated on a symptom-oriented basis until

definitive diagnosis is established. OS demands prompt immunosuppressive therapy and referral to a specialized centre where HSCT has to be performed as soon as possible. CB can be used successfully across HLA-barriers to transplant infants suffering from OS and less stringent requirements for HLA-matching due to the relative immaturity of the T-cells have to be maintained.

Conflict of interest

None.

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