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CD3+ T Cell Lineage Specific Maternal Engraftment in Pediatric Patient with Severe Combined Immunodeficiency Disorder

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Abstract: *Background:* Transplacental Maternal Engraftment (TME) is common in patients with Severe Combined Immunodeficiency Disorder (SCID), however only a few are complicated by Graft Versus Host Disease (GVHD) prior to Hematopoietic Cell Transplantation (HCT). *Objective:* We will discuss a rare case of a SCID patient with complete TME at birth who later developed pre-HCT GVHD secondary to TME. *Materials and Methods:* Peripheral blood mononuclear cells or sorted cell populations are used for TME monitoring. Chimerism testing/engraftment analysis was performed by PCR based capillary electrophoresis to detect genetic polymorphisms in short tandem repeat loci. *Results:* SCID was diagnosed on newborn screen and the patient was prematurely born at 33 weeks of gestation. The patient had GVHD secondary to TME, which involved skin, liver, gut and bone marrow along with other clinical symptoms of SCID and treated with tacrolimus and methylprednisolone. The patient was transplanted three months after birth with an HLA identical sibling donor. Partial donor engraftment was seen in myeloid cells followed by B and T cell lineages from day +42 post transplantation. Testing sorted CD4+ and CD8+ T cells at day +42 revealed that the engrafted maternal CD3+ cells were exclusively of CD4+ phenotype, which represented 15% of circulating CD4+ T cells. *Conclusion:* Based on our findings, we suggest that CD3+ lineage specific T cells, presumably CD4+, might be the main contributor for pre-HCT GVHD secondary to TME.

Keywords: Chimerism, Maternal Engraftment, SCID, GVHD, CD3+ T Cell, HCT

1. Introduction

SCID is a genetically heterogenous disorder characterized by the complete failure of T cell maturation and lack of functional T and B lymphocytes due to numerous genetic mutations [1]. SCID can be identified at birth by newborn screening; however, if untreated, infants usually suffer from severe and recurrent infections [2].

The human placenta allows for bidirectional passage of nucleated cells between mother and fetus in which mother's cells are usually eradicated by the immune system of healthy infants [3]. In SCID, the infant may lack the functional immunity to reject circulating maternal T cells, resulting in persistent transplacental maternal engraftment (TME) in up to 40% of SCID patients [4-6]. TME is common in certain types of SCID, however only 9% of them are associated with GVHD [7].

GVHD is a potentially life-threatening syndrome characterized by inflammation in different organs after allogeneic transplantation when the donor mature T cells attack the mismatched host cells. Although GVHD is commonly associated with allogeneic transplantation, it has also been noted as a complication after transfusion of nonirradiated blood products containing viable T cells, and with maternal cell engraftment in severely immunocompromised patients [8, 9]. In other studies, GVHD

was completely absent in a number of patients despite the substantial number of circulating maternal T cells, while various degrees of GVHD manifestations were present in other patients with SCID [10, 4-6].

The inconsistency and variability of GVHD in patients with TME has been reported to be associated with T cell subsets [11, 4, 10]. There was no clinical evidence of significant GVHD in SCID patients with CD8+ TME [10], whereas CD4+ TME predominantly presented in patients with skin and liver GVHD [4, 11].

In this case study, we show the engraftment analysis of a SCID patient having CD3+ lineage specific presumably CD4+ transplacental maternal T cell engraftment, which might be the main contributor of pre-HCT GVHD.

2. Materials and Methods

Chimerism testing/engraftment analysis was performed by PCR based capillary electrophoresis (CE) to detect genetic polymorphisms in short tandem repeat (STR) loci. Briefly, amplification of the STR was performed using PowerPlex 16 Human Identity Kit (Promega), and the PCR amplified fragments were then separated by size and detected by CE using ABI 3700 Genetic Analyzer (Applied Biosystems, USA). Data analysis was facilitated by a fragment analysis software (GeneMapper). DNA was extracted from patient and donor baseline peripheral blood mononuclear cells (PBMC, patient's pre-HCT sample) and patient's post-HCT sorted cells for chimerism testing/engraftment analysis. The lineage specific cell populations for CD3, CD4, CD8, CD19, CD56, CD33, and CD34 were sorted by fluorescence activated cell sorter (Becton Dickinson Aria II). High resolution HLA typing for patient, parents and one sibling were performed by long range NGS technology (Illumina, MiSeq platform) using Illumina TruSight HLA v2 Sequencing Panel and TruSight Assign analysis software.

3. Results

3.1. Retrospective Analysis of Chimerism Tests for Transplacental Maternal Engraftment in SCID Patients

We conducted a retrospective analysis of SCID patients who had chimerism testing for TME between 2011-2021. A total of 29 patients were tested for TME using either PBMC or sorted cells, including CD3+ T and CD19+ B cell populations. Five of 29 patients had detectable TME at various levels (Table 1). Of note, only one SCID patient had complete TME in PBMC at birth and developed pre-HCT GVHD. In over a month, the majority of TME was replaced by the patient's own cells. Although TME composed only 5% of the infant's PBMC, 97% of the cells were CD3+ T cells. In another two patients, only 1% - 2% of PBMC were TME. In one patient who was diagnosed with T- B+ NK- X-linked SCID, no TME was detected in PBMC, but there was a detectable TME (16%) in the sorted CD3+ T cells at 4.5 months of age. Another patient was diagnosed as SCID at 7 months with 97% TME in the sorted CD3+ T cells. These findings suggest that TME could be assessed more accurately in fractionated cell populations rather than in PBMC.

Table 1. *SCID patients with detectable Transplacental Maternal Engraftment by chimerism test at CIL in last 10 years.*

Patient	Age	Host of DNA obtained	PBMC	CD3 sorted	Diagnosis	Pre-HCT GVHD
PT-1	10 day old	Patient	0	NT	T- B- NK+ SCID	Yes
	Pre-HCT day -79	Mother	100	NT		
	1.5 month old	Patient	95	NT		
	Pre-HCT day -41	Mother	5	NT		
	2 months old	Patient	NT	3		
	Pre-HCT day -22	Mother	NT	97		
PT-2	10 day old	Patient	100	NT*	T- B+ NK- X-linked SCID	No
	Pre-HCT day -130	Mother	0	NT		
	4.5 months old	Patient	NT	84		
	Pre-HCT day -8	Mother	NT	16		
PT-3	1 month old	Patient	98	NT	SCID	NI**
	Pre-HCT	Mother	2	NT		
PT-4	8 months old	Patient	NT	3	SCID (diagnosed at 7 m. o)	NI
	Pre-HCT	Mother	NT	97		
PT-5	18 day old	Patient	99	NT	SCID	NI
	Pre-HCT	Mother	1	NT		

Fife out of 29 SCID patients had detectable TME either in PBMC or in CD3 sorted cell populations. Out of five patients with TME, only one patient had diagnosed and treated for GVHD pre-HCT. *Could not sort CD3. **NI - No information.

3.2. A Newborn SCID Patient with Complete Transplacental Maternal Engraftment

3.2.1. Pre-HCT Clinical Status of Infant

The infant was born prematurely at 33 weeks of gestation due to placental abruption and uterine rupture. On newborn screen SCID was diagnosed with likely T- B- and NK+ phenotype zero TRECs with abnormal mitogen stimulation of PHA. The chimerism test showed a complete Transplacental Maternal Engraftment (TME) at day 10 after birth. The patient had the following symptoms: intolerance to oral intake, skin rash, and

elevated liver enzymes demonstrating presumed GVHD of gut, skin, and liver secondary to maternal engraftment. The patient was treated with tacrolimus and methylprednisolone followed by HCT from an HLA identical sibling at 3 months after birth.

3.2.2. Pre-HCT Chimerism

Pre-HCT Chimerism testing identified 100% maternal cells in the infant's PBMC at day 10 after birth. At day 48 after birth, 95% of maternally engrafted cells were replaced by host cells in the infant's unsorted PBMC. When the chimerism test was performed at day 67 of birth, 100% of CD19+ B cells and CD33+ myeloid cells were of host origin, however 97% of CD3+ T cells and 4% of CD56+ NK cells were determined to be maternal origin. (Table 2).

Table 2. *Pre-HCT Chimerism.*

Age	Pre-HCT Sample date	Host of DNA obtained	Sample Source tested				
			PBMC	CD3	CD56	CD19	CD33
10 day old	Pre-HCT Day -79	Patient	0				
		Mother	100				
48 day old	Pre-HCT Day -41	Patient	95				
		Mother	5				
67 day old	Pre-HCT Day -22	Patient		3	96	100	100
		Mother		97	4	0	0

SCID patient's age is shown by days after birth. Pre-HCT sample date is counted backward from transplant day 0. Chimerism tests were performed using unsorted PBMC at -79 and -41 days pre-HCT and sorted cells at day -22 pre-HCT. Majority of engrafted maternal cells were CD3+ T cells at day -22 pre-HCT.

3.2.3. Post-HCT Chimerism

At day +24 post-HCT, maternal engraftment of CD3+ T cells declined to 39% and further declined to 9% at day +42 post-HCT. At one time point (day +42 post-HCT), the chimerism test was conducted using CD4+ helper and CD8+ cytotoxic T cell subpopulations. Interestingly, the CD4+ T cell subset presented mixed chimerism consisting of 82% host, 15% maternal and 3% donor origin, however all of the CD8+ cytotoxic T cells were of host origin. Maternal engraftment of CD3+ T cells completely disappeared, replaced by host at day +83, whereas sibling donor engraftment of CD3+ T cells started at day +110 post-HCT. In contrast, maternally engrafted CD19+ B cells, CD33+ myeloid cells, and CD56+ NK cells completely disappeared, replaced by host cells soon after HCT. Sibling donor engraftment started from day +83 post-HCT, gradually increasing over time (Table 3).

Table 3. *Post-HCT Chimerism.*

Patient Age	Pre-HCT Sample date	Host of DNA obtained	Sample Source tested (by percentage)						
			CD3	CD4	CD8	CD56	CD19	CD33	CD34
114 days old	Post-HCT day 24	Patient	61	NT	NT	100	100	100	NT
		Mother	39	NT	NT	0	0	0	NT
		Donor	0	NT	NT	0	0	0	NT
132 days old	Post-HCT day 42	Patient	91	82	100	100	97	73	NT
		Mother	9	15	0	0	0	0	NT
		Donor	0	3	0	0	3	27	NT
146 days old	Post-HCT day 56	Patient	98	NT	NT	100	86	59	52
		Mother	2	NT	NT	0	0	0	0
		Donor	0	NT	NT	0	14	41	48
173 days old	Post-HCT day 83	Patient	100	NT	NT	92	77	36	55
		Mother	0	NT	NT	0	0	0	0
		Donor	0	NT	NT	8	23	64	45
200 days old	Post-HCT day 110	Patient	94	NT	NT	81	73	36	33
		Mother	0	NT	NT	0	0	0	0
		Donor	6	NT	NT	19	27	64	67
409 days old	Post-HCT Day 547	Patient	57	NT	NT	8	36	1	NT
		Mother	0	NT	NT	0	0	0	NT
		Donor	43	NT	NT	92	64	99	NT

NT-Not tested. Patient age is shown by days. CD3+ TME is disappeared by day +83 post-HCT. Donor CD3+ T cell engraftment had started by day +110 post-HCT, while CD19, CD33, CD34 and CD56 engraftments had started as early as day between day +42 and +83 post-HCT, respectively.

3.2.4. Post-HCT Clinical Status

At day +42 post-HCT, the patient had normal TREC copies (>9000) and with low CD3, CD4 and CD8 T cells consistent with pan T cell Lymphopenia, which stayed stable or steadily rising in subsequent tests. In three months post-HCT patient had mildly decreased response to mitogen PHA compared to control. There was no evidence of skin or liver GVHD, however ongoing intermittent emesis and increasing loose stool output was noted the first few months following HCT. Skin rash was detected 2-3 months post-HCT, which needed differential diagnosis to rule out non-GVHD causes. Skin biopsy revealed that spongiotic dermatitis with parakeratosis and

scattered apoptotic keratinocytes; GVHD was present but was unlikely the sole cause for rash. Peak grade GVHD (S4, G1, L0) with late acute skin flare and mild gut symptoms were diagnosed 6 months post-HCT, which was successfully managed with tacrolimus and steroid. Currently, the patient is clinically stable and has no GVHD.

4. Discussion

Maternal engraftment is a common feature in SCID patients. It was commonly accepted that the presence of large amounts of maternal T cells in SCID patients only occurs if host T cells are lacking. However, recent findings of long-term coexistence of engrafted maternal T cells and autologous T cells in a SCID patient with a Janus kinase (JAK) 3 mutation [12] and in a patient with mild Omenn's Syndrome phenotype [13] have changed that thinking.

Maternal DNA sequences have been found in fetal blood by using very sensitive PCR based methods able to detect 1 maternal cell in 100-100,000 fetal cells [3]. Several studies showed that the maternally derived engrafted T cells, ranging from 10 to several thousand/ml of blood, are functionally incompetent and show limited or no proliferative response to mitogens. In addition, maternal T cells can be stimulated via CD3/TCR, which could be suggestive that transplacental passage of very small number of T cell could successfully expand in the host. However, those transplacental maternal cells were not responsive to recall antigens and less clonal as well as restricted. These findings suggest that limited TCR diversity is a common feature of maternal T cells in SCID patients [14]. Of note, early studies had shown that transplacental maternal T cells in SCID patients showed no evidence of inducing GVHD after haploidentical Bone Marrow Transplantation as well as apparently failing to protect the host against a variety of infections [14-16].

Although a number of studies support the maternal T cells in SCID patients as being non-functional [6, 15, 16], rare cases show that engrafted maternal T cells might persist for a long time leading to partial reconstitution of immune function, which provides some degree of immunity to protect the child from severe infections and delayed clinical presentation of SCID [12, 17]. In the majority of cases, SCID patients with maternal T cell engraftment are asymptomatic, but approximately 30-40% of them have mild signs and symptoms such as eosinophilia, elevated liver enzymes with periportal T cell infiltration and erythema with skin T cell infiltration. These hepatic and cutaneous manifestations are similar to those observed during GVHD development after HCT [4].

Several studies described the phenotype of maternally engrafted T cells. Cattaneo et al presented that co-existing maternally derived T cells in SCID patients with Jak 3 mutation were CD4+ and CD8+ CD45- effector memory (CD62L-) and central memory (CD62L+) phenotypes and were non-proliferating (Ki67-) as well as non-active (HLA-DR-) [12]. However, the maternally engrafted T cells retained short-term functional capacity in vitro by vigorously diluting CFSE [12], which was contrary to reports of poor in vivo proliferation of maternally engrafted cells [4]. A study conducted with a large cohort of SCID patients demonstrated that manifestation of skin GVHD were prominent in patients who had predominantly CD4+ maternal T cells, whereas in patients with mild and/or no signs of GVHD, the maternal T cells were predominantly CD8+ phenotype [4]. In addition, maternal T cells in SCID patient showed a slightly reduced number of CD3+ cells consisting only of CD4+ and not CD8+ cells, a lack of B cells and a high number of cells expressing HLA-DR, pointing to an activated state of the CD4+ T cell population [14]. Furthermore, Conley et al. presented two male SCID patients with maternally engrafted T cells predominantly bearing a surface marker of cytotoxic/suppressor cells with fewer helper T cells, however both patients had no clinical evidence of significant GVHD [10]. In a SCID patient having chronic GVHD affecting liver and skin, the maternally engrafted CD8+ T cell receptor (TCR) γ/δ + clone was dominant, however combined immunohistologic and molecular genetic data revealed that this particular TCR γ/δ+ CD8+ maternal T cells had minor contribution to the pathogenesis of GVHD in the liver [11]. The study reported that patchy lymphocytic infiltrates present in portal fields were predominantly TCR α/β+ CD4+ maternal T cells, whereas only 3% of the T cells were TCR γ/δ + CD8+ maternal T cells. However, the latter were found up to 14% of skin biopsy lymphocytic infiltrates [11].

Recent studies demonstrated that SCID patients with 100% maternal cells present a higher fraction of functional CD4+CD25+Foxp3+ regulatory T cells than SCID patients with barely detectable maternal cells, conferring a high-tolerance capacity that appears to represent a toleration advantage beside the severe immunodeficiency [18]. Lev at al. also detected a greater number of circulating regulatory T cells in the maternally engrafted T cell population, co-existing with the patient's autologous T cells. The latter had no CD4+CD25+Foxp3+ expression whatsoever [19]. CD4+CD25+Foxp3+ regulatory T cells are thought to protect against GVHD by inducing and maintaining allogeneic tolerance [20]. Therefore, the less clonal feature of maternal T cells with lack of alloreactivity toward the child's antigens might explain the asymptomatic state or less severe GVHD cases in SCID patients who have maternal T cell engraftment [21].

Our retrospective analysis showed that 17% of SCID patients tested for chimerism had detectable TME at various levels. More compelling results confirming TME in SCID patients were seen in CD3+ sorted cell populations rather than in unsorted PBMC. Of note, only one patient had 100% TME detected in PBMC at birth and this patient was the only one diagnosed with GVHD prior to HCT. Pre-HCT chimerism tests showed 97% of CD3+ T cells and only 4% of CD56+ NK cells were maternal origin, suggesting that pre-HCT GVHD was predominantly caused by CD3+ T cells. CD56+ NK cells are generally not considered to cause GVHD, with the exception of $CD56^{bri}$ immature NK cells

that may play an important role in pathogenesis of GVHD [22]. Cell surface markers were not tested in our case, however if GVHD existed, we assume that maternally engrafted NK cells were most likely composed of mature cells and therefore would have had a minor contribution prior to HCT.

In this particular case, CD4+ and CD8+ sorted T cells were tested for chimerism at day 42 post-HCT. Notably, the CD4+ population consists of a unique mixed chimerism profile of 3 different individuals (patient, mother and donor). Although, the percentage of CD3+ TME dramatically decreased to 9% at day 42 compared with day 24 post-HCT, they exclusively expressed CD4+ helper T cell phenotypes, which supports previous studies [4, 11]. Interestingly, 3% of CD4+ but CD3- unconventional T cell engraftment from the donor was also detected. The CD4+CD3- unconventional T cells, also called as "Lymphoid Tissue Inducer: LTi" or "Innate like T cells", are known to provide survival signals to innate and adaptive lymphocytes via expression of the TNF family members and can be expressed on embryonic as well as adult lymphocytes [23-26]. Therefore, it is not unusual that we have detected CD4+CD3- donor engraftment in sorted cells prior to starting CD3+ donor T cell engraftment.

5. Conclusion

Here we present a rare case of a SCID patient with 100% TME at birth, who developed GVHD in skin, liver, gut and bone marrow before HCT. Pre-HCT, GVHD secondary to TME, monitored by chimerism tests/engraftment analysis on PBMC or sorted cell populations, revealed that TME was exclusively CD3+ lineage specific T cells. Follow up engraftment monitoring showed that CD3+ lineage specific T cells in TME were presumably CD4+ helper T cells. Taken together, our data supports previously reported findings that GVHD manifestation was prominent in SCID patients with CD4+ TME. Different subpopulations of maternal T cells leading to various manifestations of GVHD remain to be investigated.

Abbreviations

SCID Severe Combined Immunodeficiency Disorder; TREC T-cell receptor excision circles; PHA phytohemagglutinin; GVHD graft-versus-host-disease; STR short tandem repeats; TME transplacental maternal engraftment; HCT hematopoietic cell transplantation; CE capillary electrophoresis; TCR T cell receptor.

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